Organocatalytic Asymmetric Direct Vinylogous Aldol Reactions of 2-Furanone and Application in the Synthesis of (+)-L-733,060, (+)-CP-99,994, (2*S*,3*R*)-3-Hydroxypipecolic Acid and (+)-Febrifugine

by

© **Eldho K. Paul**

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

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St. John's, Newfoundland

May 2014

To my family

ABSTRACT

The organocatalytic, direct vinylogous aldol reaction (ODVA) of 2-furanone (*γ*-crotonolactone) is of interest because the reaction provides direct access to *γ*-substituted butenolides, an important structural motif in several natural products and biologically active compounds. We have observed that this reaction is catalyzed by chiral aminothioureas and aminosquaramides. A detailed investigation of this method is described in Chapter 2. The ODVA reaction of *γ*-crotonolactone with aldehydes can be used for the synthesis of substance P receptor antagonist piperidines (+)-L-733,060 and (+)-CP-99,994, and also for the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid, which is a component of tetrazomine, an antitumor agent and an antibiotic. These results are presented in Chapter 3. This methodology is also useful for the total synthesis of the antimalarial alkaloid (+)-febrifugine and a formal synthesis of (+)-halofuginone, an antimalarial agent. The results of this work are described in Chapter 4.

ACKNOWLEDGEMENTS

First and foremost, I'd like to thank my thesis advisor, Professor Sunil V. Pansare, for his guidance, endless support, enthusiasm and encouragement throughout my doctoral studies. From the first day, his door was always open when I needed to discuss any topic, no matter how random or obscure. I am extremely grateful for his guidance, patience and creativity in approaching chemical problems.

I express my gratitude to other members of my thesis committee, Professor Yuming Zhao and Professor Ray Poirier for providing me their support, valuable comments and suggestions over the years. It's been a true pleasure to interact with Professor Graham Bodwell and Professor Paris Georghiou. They have provided me with helpful discussions, support and encouragement during the program.

I would like to thank Professor K. K. Balasubramanian, a former Professor at the Indian Institute of Technology, Madras, and my research supervisor at Shasun Research Center Chennai. He was tremendously important in my decision to undertake my Ph.D studies. Without his support, I wouldn't have pursued my higher studies.

During my doctoral programme I have had the privilege of working with a number of exceptionally wonderful people and I would like to take the opportunity to thank them individually. Dr. Rajinikanth Lingampally was the only senior-most person in our lab when I started my programme. Thank you so much Dr. Rajini for the great support in the beginning years. He was always there for help, with so much patience. My special thanks to Mr. Rajendar Dyapa, Mr. Kaivallya Kulkarni, and Mr. Rakesh Thorat, for their support and encouragement in the lab. As we always say, this is the best time in our life and it's never going to come back. I always cherish the memories we had inside

and outside the lab. I thank, Mr. Guru Moorthy, Mr. Ryan Hughes, Mr. Tim Morgan, Mr. Adam Hefferman, Mr. Wilson Humphries and Ms. Robyn Penney for their support. Apart from my lab-mates, the help and support from MUN colleagues from other research groups is greatly appreciated. Also, I thank all my friends in St. John's who supported me throughout my stay.

I'd like to thank Ms. Julie Collins and Dr. Celine Schneider for the training and assistance with NMR spectroscopy, Ms. Linda Winsor for the training and support with mass spectrometry, and Mr. Brent Myron for the support with IR spectroscopy.

I would like to thank Mr. Dave Murphy for his help with computer-related matters. I thank Ms. Mary Flinn, Ms. Rosalind Collins, Ms. Ebony Penny, Ms. Gina Jackson and the late Ms. Viola Martin in the Chemistry department for their assistance with administrative matters. I thank Mr. Steve Ballard, Ms. Bonita Smith for providing store-room support. I would like to extend thanks to colleagues in the teaching labs, Mr. Patrick Hannon, Mr. Cliff McCarthy, Ms. Nathalie Vanasse, Ms. Anne Sheppard, Mr. Dave Stirling and Ms. Hyma Naidu for their wonderful support.

I also wish to thank the Department of Chemistry, Memorial University of Newfoundland, the Natural Sciences and Engineering Research Council of Canada, and Canada Foundation for Innovation for financial support.

Finally, I want to give my deepest thanks to my family, especially my mom and dad. Thanks to my sisters for their continuous support throughout my life. This thesis certainly would not have been possible without the love and encouragement from them.

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List of Schemes

List of Abbreviations and Symbols

Ac	acetyl
ADH	asymmetric dihydroxylation
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Boc	*tert*-butoxycarbonyl
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
dr	diastereomeric ratio
$(DHQ)_2$-PHAL	hydroquinine 1,4-phthalazinediyl diether
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess

EI	electrospray ionization
eq.	equivalent(s)
Et	ethyl
g	gram(s)
h	hour(s)
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	Hertz(s)
IBX	2-iodoxybenzoic acid
IR	infrared
i-Bu	isobutyl
J	coupling constant
L	ligand
LAH	lithium aluminium hydride
M	molar
M+	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
MOM	methoxymethyl ether

MsCl	methanesulfonyl chloride
mp	melting point
MS	mass spectrum
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
ODVA	organocatalytic direct vinylogous aldol
OVMA	organocatalytic vinylogous Mukaiyama aldol
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTSA	*para*-toluenesulphonic acid
pyr	pyridine
RCM	ring-closing metathesis
rt	room temperature
SES	(2-Trimethylsilyl)ethanesulfonyl
SmI_2	samarium iodide
t-Bu	*tert*-butyl
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*p*-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
UHP	urea hydrogen peroxide
UV	ultraviolet
VMA	vinylogous Mukaiyama aldol
^{o} C	degree Celsius
δ	chemical shift (spectroscopy)
α	alpha
β	beta
γ	gamma
δ	delta
ε	epsilon
π	pi

CHAPTER 1

Introduction

This chapter is based on the following publication (mini-review):

Pansare, S. V.; Paul, E. K. *Chem*. *Eur*. *J*. **2011**, *17*, 8770-8779.

Contributions of authors

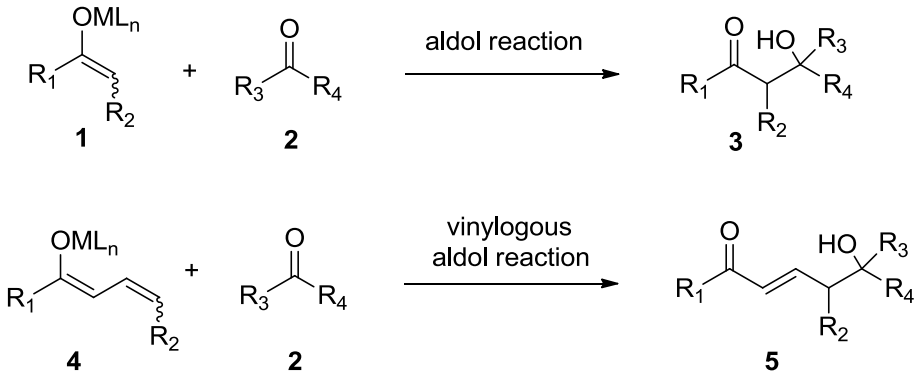
S. V. Pansare: research supervisor, literature review, manuscript preparation.

E. K. Paul: literature review, manuscript preparation.

CHAPTER 1

Introduction

The aldol reaction is one of the most powerful synthetic tools in organic chemistry for carbon-carbon bond formation. Within the domain of aldol processes, the vinylogous extension is of considerable interest. In 1935, R. C. Fuson introduced the principle of vinylogy[1] to explain the effect of a functional group at a position in the molecule that is separated from the functional group by a double bond. This concept allows for the transmission of electronic effects through a conjugated π-system of a carbon–carbon double bond. This "vinylogous extension" has been applied to the aldol reaction by employing *α,β*-unsaturated carbonyl compounds as the nucleophilic component (Scheme 1.1).[2a]



Scheme 1.1. Classical aldol *vs*. vinylogous aldol reactions.

Over the years, the vinylogous aldol reactions of silyloxy dienes (vinylogous Mukaiyama aldol reaction) as the nucleophiles have been thoroughly studied. Most of the

vinylogous Mukaiyama aldol (VMA) reactions use metal-based catalysts, with several reviews available on this topic.[2] In recent years the use of non-metal-derived catalysts (boron derived catalysts and bisphosphoramide/$SiCl_4$ catalysts) and organocatalysts (metal-free organic catalysts) for the VMA reaction has proven to be successful. There are a few reviews available for the non-metal-derived catalysis,[2a,3] as well as the organocatalytic version.[4] In terms of atom economy, the organocatalytic direct vinylogous aldol (ODVA) reaction, which uses unmodified aldehydes and ketones as nucleophiles, is the most attractive version even though this strategy can be limited by regioselectivity issues associated with the dienolate nucleophiles.[5]

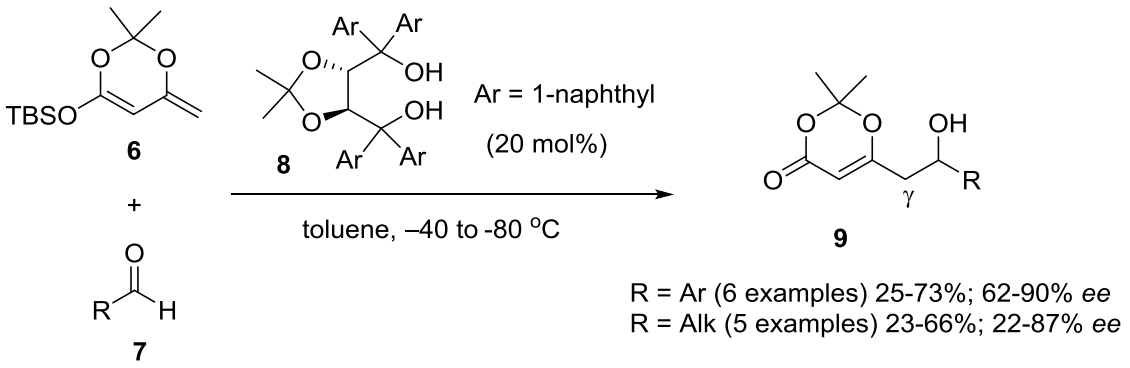
1.1 The organocatalytic vinylogous Mukaiyama aldol (OVMA) reaction

The interest in OVMA reactions is mainly due to the products being of great importance in natural product synthesis.[2,3a] With this backdrop, ample research efforts have been directed towards the development of efficient organocatalysts for asymmetric vinylogous aldol reactions. The OVMA reactions can be classified into two groups: 1) OVMA reactions of cyclic silyloxydienes, and 2) OVMA reactions of acyclic silyloxydienes.

1.1.1 OVMA reactions of cyclic siloxydienes

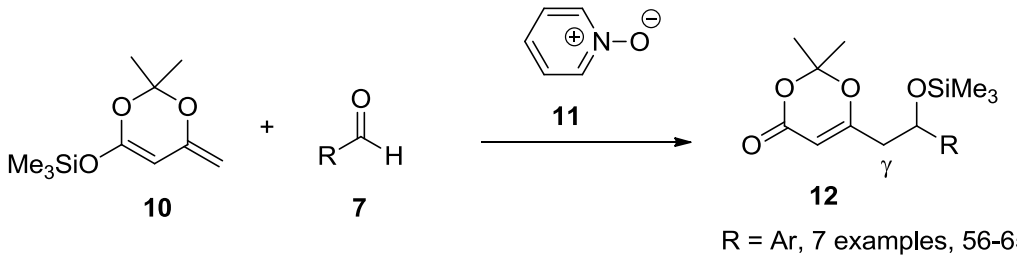
Rawal and co-workers[6] reported the first example of an organocatalyzed addition of siloxydiene **6** (Scheme 1.2) to aldehydes using various alkaloids and chiral diols as catalysts. Preliminary studies with 2-nitrobenzaldehyde as the electrophile identified the

tartrate-derived TADDOL **8** (*α*,*α*,*α*',*α*'-tetraaryl-1,3-dioxolane-4,5-dimethanol) as a promising catalyst. Thus, under optimized conditions, the siloxydiene **6** reacts with a variety of aldehydes in presence of a catalytic amount of TADDOL **8** to provide the vinylogous aldol adducts **9** (Scheme 1.2) in poor to good yields (23-73%) and enantioselectivity (22-90% *ee*). In general, aromatic aldehydes gave better results than aliphatic aldehydes in terms of yield and enantioslectectivity. Also, all of the reactions showed complete *γ*-selectivity.



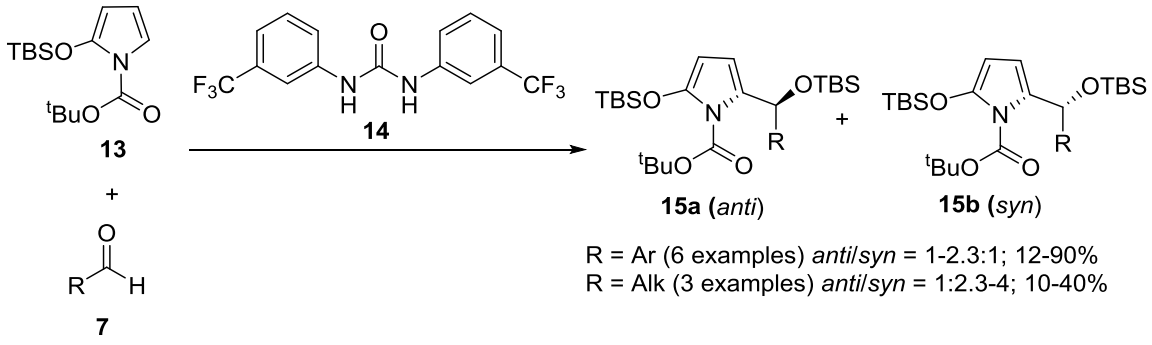
Scheme 1.2. The first asymmetric OVMA reactions catalyzed by TADDOL.

Complementary to the TADDOL catalyzed process, Scettri and Acocella[7] reported the VMA reaction of siloxydiene **10** catalyzed by a Lewis base (Scheme 1.3). Initial experiments with the diene **10** and 4-methylbenzaldehyde indicated that pyridine *N*-oxide is the catalyst of choice among other catalysts such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF) and hexamethylphosphoramide (HMPA). A variety of aromatic aldehydes provided the aldol adduct **12** in moderate yields. The asymmetric version of this reaction was not investigated in this study.



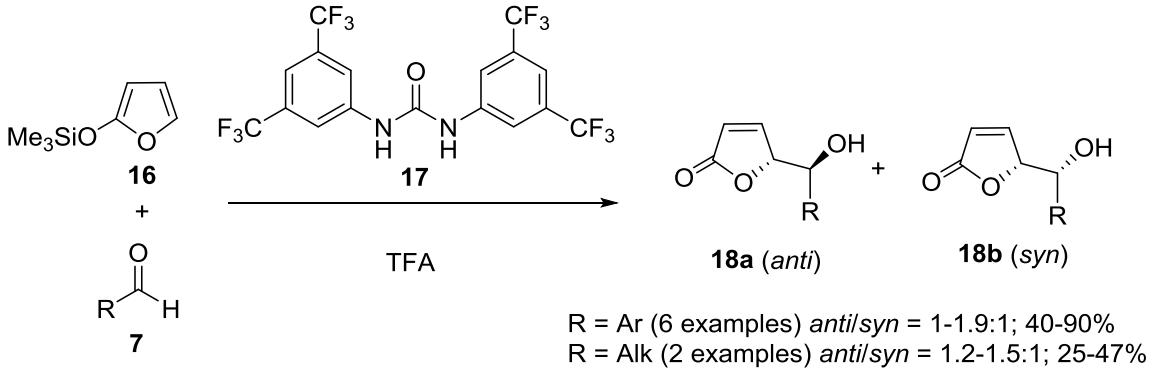
Scheme 1.3. The Lewis base catalyzed OVMA reaction reported by Scettri and Acocella.

Zanardi and Casiraghi[8] have developed a novel variant of the classical Lewis acid catalyzed vinylogous Mukaiyama aldol reaction using *tert*-butyl 2-[(tert-butyldimethylsilyl)oxy]-1*H*-pyrrole-1-carboxylate **13** as the conjugate donor. Subsequently, the organocatalytic version of their reaction catalyzed by various ureas and thioureas was reported by Soriente.[9] By using **13** as the vinylogous donor, structurally and stereochemically diverse *γ*-substituted-*α,β*-unsaturated lactam silyl ethers were obtained in high yields (Scheme 1.4). Optimization studies revealed that the urea **14** was the catalyst of choice and the OVMA reaction provided a mixture of *anti* (**15a**) and *syn* (**15b**) aldol products in poor to good yields. The asymmetric version of this reaction was not investigated in this study.



Scheme 1.4. The OVMA reaction of **13** by urea catalyst **14**.

The OVMA reactions of siloxyfurans **16** as nucleophiles were first reported by Soriente[10] in 2006. Several aromatic aldehydes were examined for the VMA reaction using 1,3-bis-(3,5-(trifluoromethyl)phenyl)urea **17** (10 mol%) as catalyst at room temperature and the γ-butenolide adducts were obtained in poor to good yields (Scheme 1.5). The diastereoselectivity of the reaction was moderate (1.9:1 to 1:1), favoring the *anti* diastereomer in some cases.

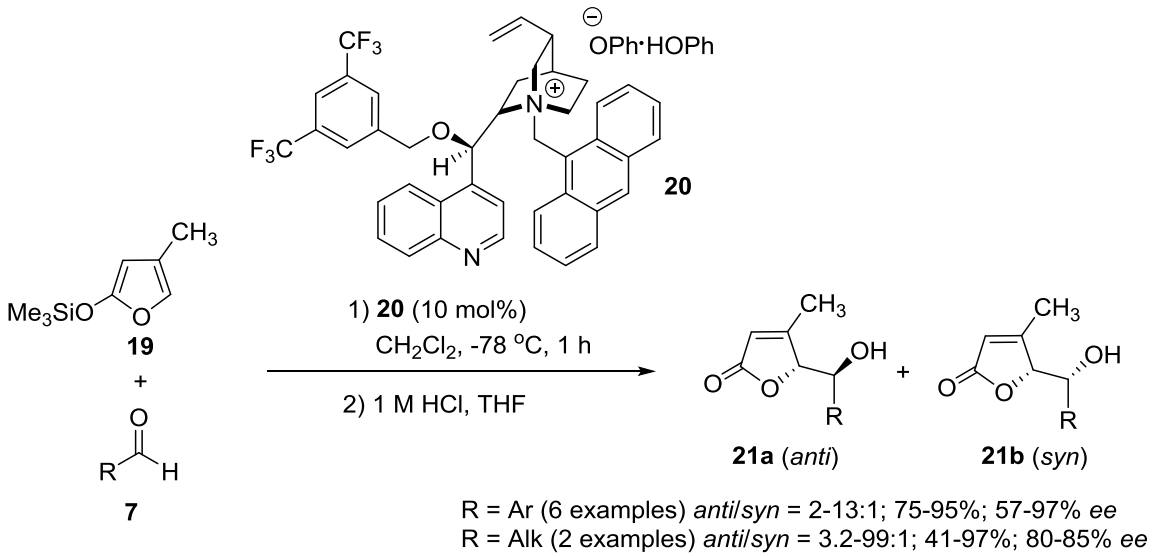


Scheme 1.5. Diarylureas as catalysts for the OVMA reaction of trimethylsiloxyfuran.

The same group reported the OVMA reaction of 2-(silyloxy)furan with aromatic as well as aliphatic aldehydes using calixpyrrole[11] derivatives as catalysts. Calixpyrroles are known for their ability to bind anions and neutral molecules by multiple hydrogen-bonding interactions with the pyrrole NH functionality. A number of calixpyrroles were tested as catalysts, but these reactions resulted in low to moderate yields (15-70%) and moderate diastereoselectivities (2.3-4:1).

The first enantioselective version of the OVMA reaction of a 2-(silyloxy)furan with a variety of aldehydes was reported by Mukaiyama and co-workers.[12] This protocol

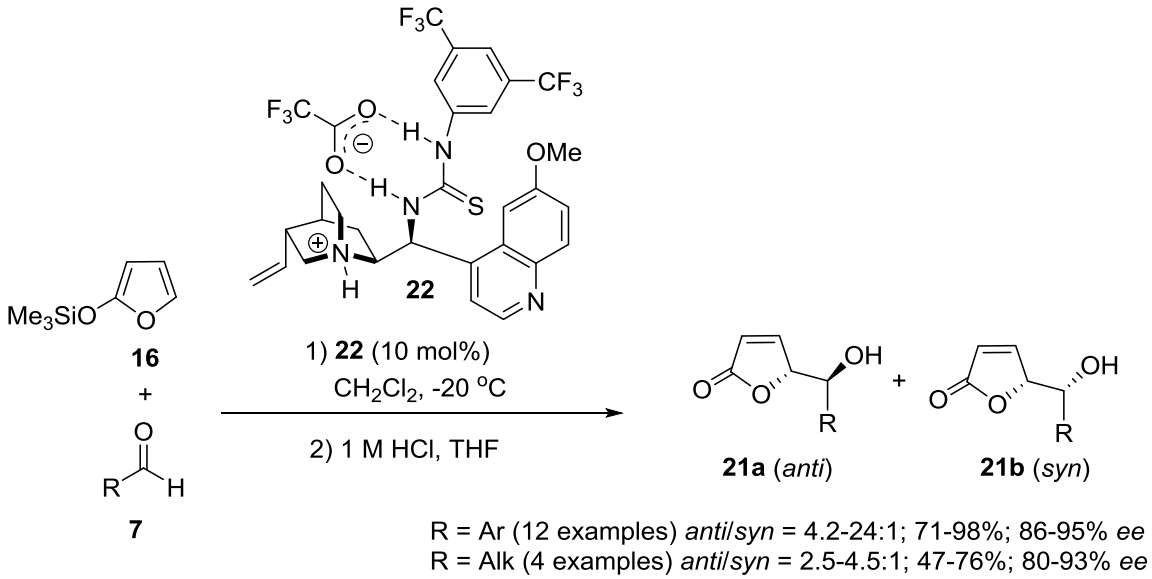
relies on the cinchonidine-derived quaternary ammonium phenoxide **20** as the organocatalyst (Scheme 1.6). Preliminary studies with trimethylsiloxyfuran and all isomers of methyl-2-(trimethylsiloxy)furan as nucleophiles showed that 4-methyl-2-(trimethylsiloxy)furan **19** is the best nucleophile in terms of yield, diastereoselectivity and enantioselectivity. Reactions with a series of aromatic and a few aliphatic aldehydes were examined. These reactions proceeded with poor to excellent diastereoselectivies (2:1 to 99:1), and the enantioselectivities of these reactions were moderate to excellent (57-97% *ee*).



Scheme 1.6. Enantioselective OVMA reactions catalyzed by cinchonidine salt **20**.

Deng *et al.*[13] examined cinchona alkaloid salts as catalysts for the OVMA reaction of 2-(silyloxy)furan with various aldehydes (Scheme 1.7). The salt of quinine derived thiourea with trifluoroacetate **22** was identified as the catalyst of choice. The reaction was *anti* selective, and both aromatic, as well as aliphatic aldehydes gave

moderate to excellent yields (47-98%). In general, the diastereoselectivities and enantioselectivities with aromatic aldehydes (4.2:1 to 24:1 d.r.; 86-95 % *ee*) were much better than those observed with aliphatic aldehydes (2.5:1 to 4.5:1 d.r.; 80-93% *ee*).

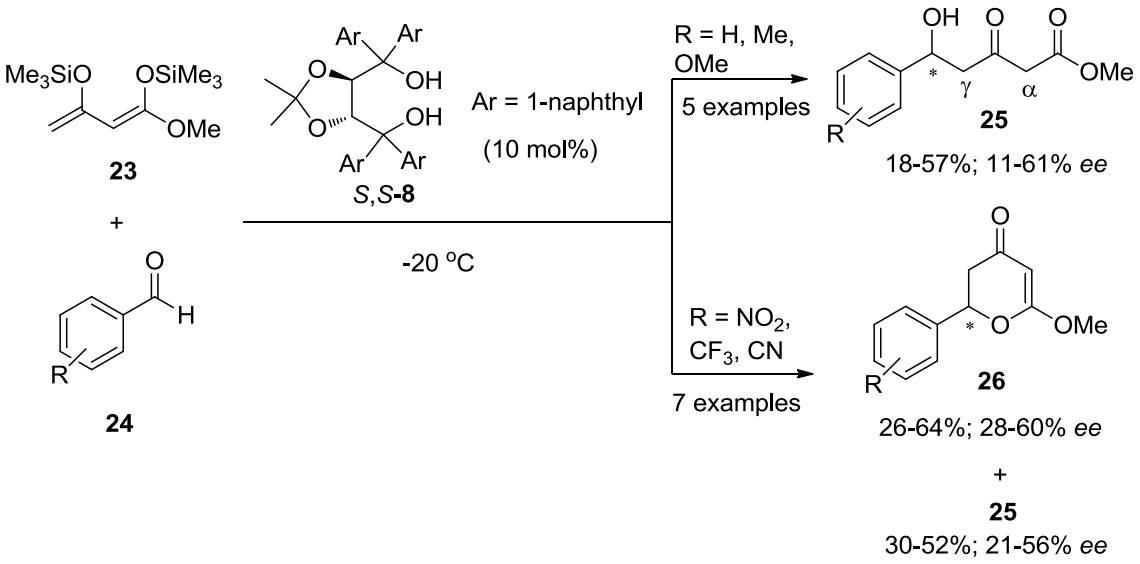


Scheme 1.7. OVMA reaction catalyzed by quinine derived aminothiourea salt.

In a related study, Wang and co-workers[14] have developed an asymmetric OVMA reaction of 2-(silyloxy)furan with aldehydes in the presence of a quinine-derived catalyst (free base of **22**). The results of this study are similar to those obtained by Deng *et al.* These reactions are conducted in chloroform at -20 ^{o}C. In general, the diastereoselectivities and enantioselectivities (1.5:1 to 9:1 d.r.; 84-91% *ee*) were similar to those obtained with the trifluoroacetate salt **22**.

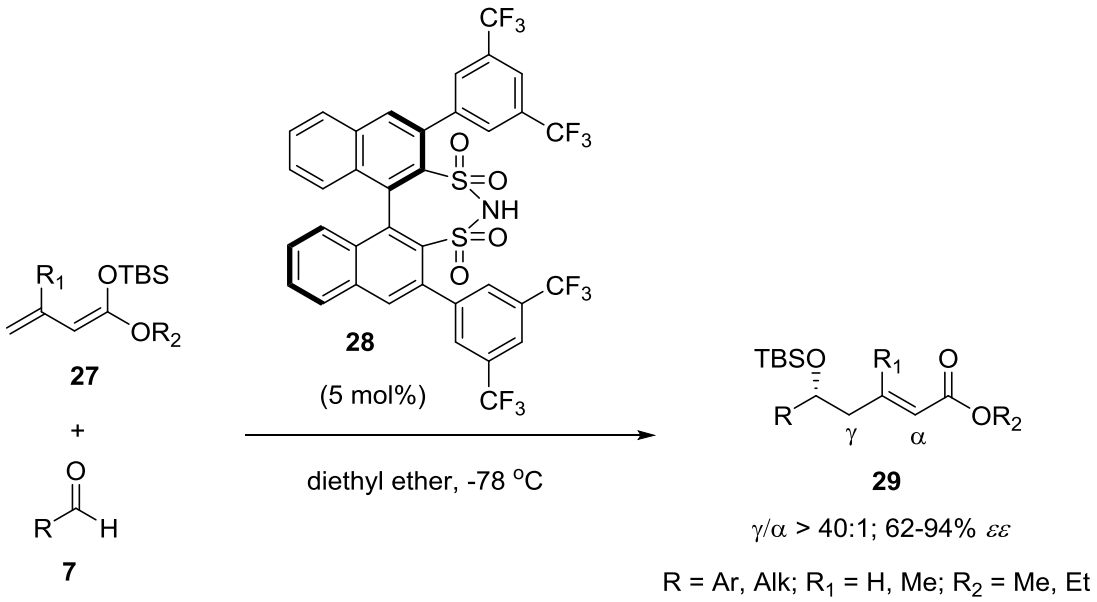
1.1.2 OVMA reactions of acyclic siloxydienes

So far, the use of acyclic siloxydienes as nucleophiles in the VMA reaction under organocatalytic conditions has been less explored. Only a few examples are known using acyclic siloxydienes as nucleophiles. Villano and Scettri[15] have utilized Chan's diene **23**[16] as the vinylogous donor. In this study, several aromatic aldehydes were used to provide the vinylogous aldol product **25** (Scheme 1.8). Notably, all these reactions proceeded with complete γ-selectivity. Interestingly, in the case of electron-poor aldehydes the chiral pyran-4-ones **26** were also obtained, along with the expected VMA adduct **25.** The authors suggest that **26** is obtained by a hetero-Diels-Alder reaction of the diene and the aldehyde.



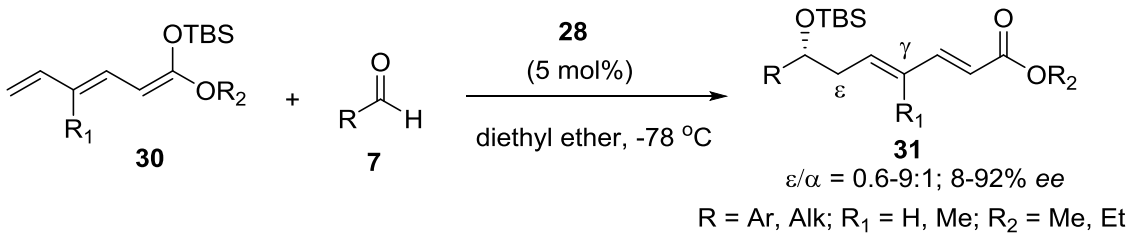
Scheme 1.8. The OVMA reaction catalyzed by TADDOL.

List *et al.*[17] developed an improved OVMA reaction using a variety of disulfonimides as catalysts. The diene **27** reacted with a variety of aldehydes to generate aldol products **29** in a highly regioselective (γ/α > 40:1) manner (Scheme 1.9).



Scheme 1.9. Disulfonimide catalyzed OVMA reaction.

In addition to the vinylogous aldol reaction, the bisvinylogous mode[17] of the reaction was also investigated (Scheme 1.10). These were the first examples of organocatalytic bisvinylogous aldol reactions, which proceeded with good enantioselectivity (up to 92% *ee*). The ε-product **31** was obtained with an all *E* configuration. Many aldehydes were tested and the optimized reaction conditions were particularly suitable for aromatic and cinnamaldehydes. Most interestingly, the γ-adducts were not detected in any of the reactions.



Scheme 1.10. Disulfonimide catalyzed bisvinylogous aldol reaction.

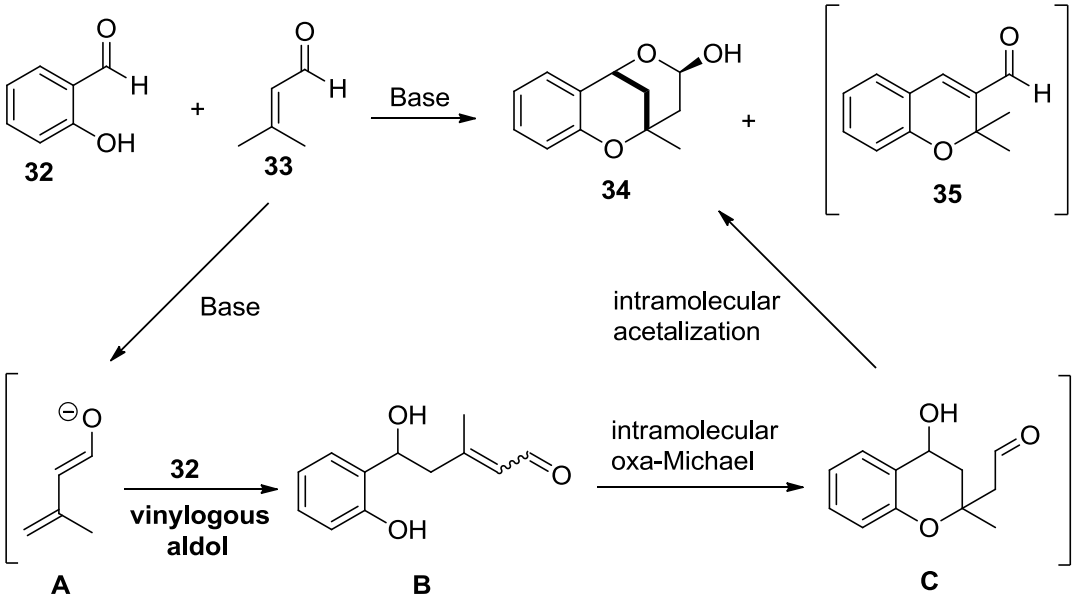
1.2 Organocatalytic direct vinylogous aldol (ODVA) reaction

The organocatalytic direct vinylogous aldol (ODVA) reaction is a more attractive version in terms of atom economy.[2] There are several challenges in controlling diastereoselectivity, enantioselectivity, chemoselectivity and regioselectivity associated with these reactions. So far, ODVA reactions are less explored and only a few studies have examined the application of unmodified *α,β*-unsaturated aldehydes as nucleophiles.

1.2.1 ODVA reactions of acyclic dienes

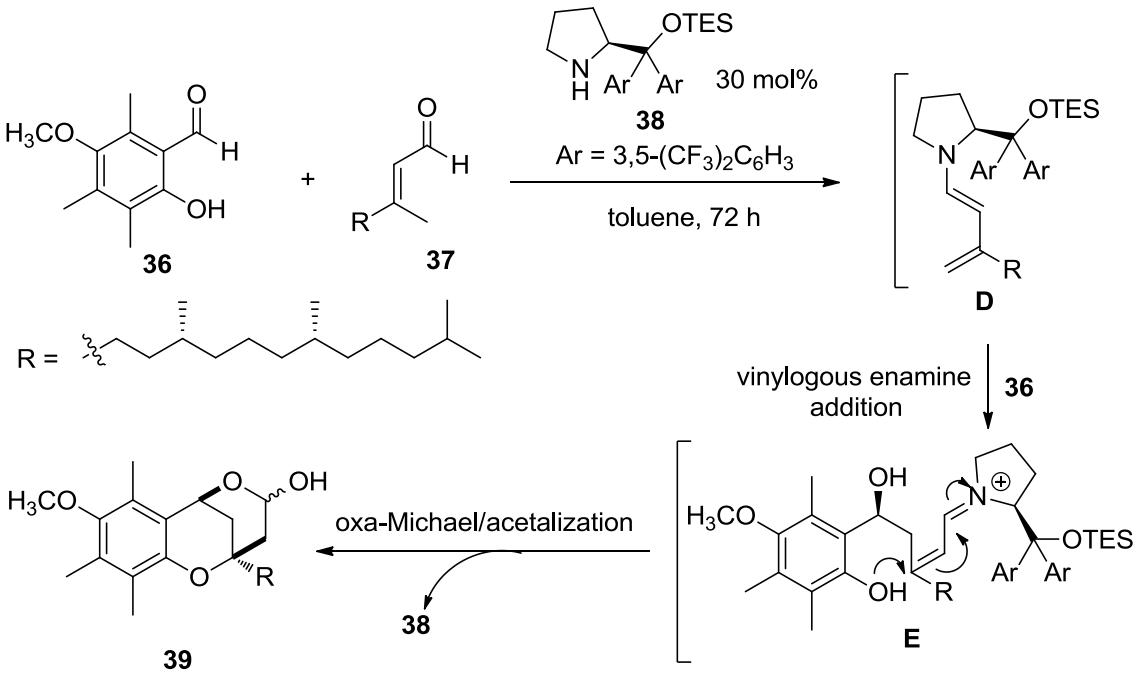
Bräse and coworkers[18] reported an ODVA reaction of salicylaldehyde **32** and senecialdehyde **33**, employing DABCO as the catalyst (Scheme 1.11). The tricyclic hemiacetal **34** was obtained by initial deprotonation of the senecialdehyde **33** at the *γ*-methyl group followed by the vinylogous aldol reaction of the resulting dienolate with salicylaldehyde **32**. An intramolecular oxa-Michael addition of the aldol adduct followed by intramolecular acetalization generated **34**. Optimization of the reaction conditions revealed that the use of sodium carbonate resulted in **35** as the major product, whereas the use of triethylamine as base provided **34** as the major product. A variety of 2-

hydroxybenzaldehydes were converted either to the tricyclic hemiacetal **34** (10 examples, up to 61% yield) or the chromenes **35** (8 examples, up to 81% yield).



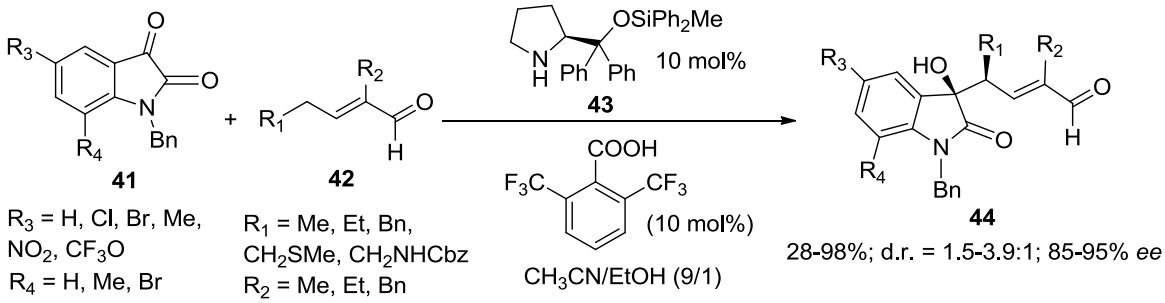
Scheme 1.11. The base promoted vinylogous aldol reaction of senecialdehyde.

In a related study, Woggon[19] examined the chiral pyrrolidine mediated vinylogous aldol reaction of an aliphatic α,β-unsaturated aldehyde and this methodology was used for the synthesis of α-tocopherol. Reaction of aldehyde **36** with phytenal **37** in the presence of a diarylprolinol catalyst **38** generated tricyclic hemiacetal **39** through a series of steps such as iminium ion formation, vinylogous aldol reaction, intramolecular oxa-Michael addition and acetalisation (Scheme 1.12).



Scheme 1.12. A vinylogous aldol route to **39**.

Recently, Melchiorre[20] reported the ODVA reaction of α-substituted α,β-unsaturated aldehydes with isatins (Scheme 1.13). The reaction provided 3-substituted 3-hydroxyoxindol derivatives **44** with good stereocontrol. Notably, these reactions proceeded with very high γ-selectivity.

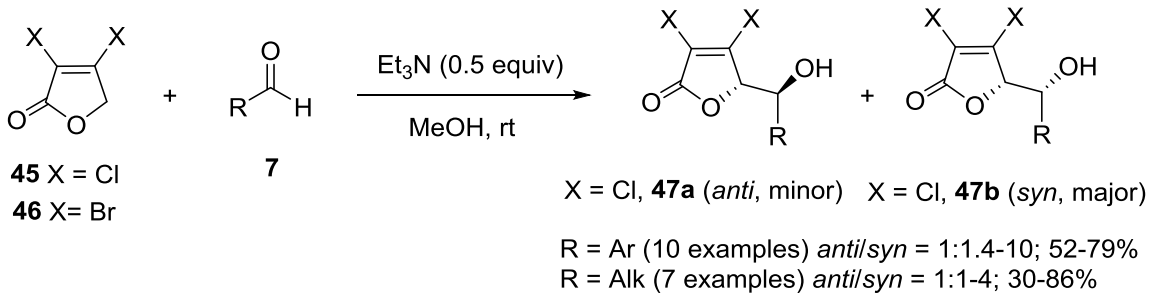


Scheme 1.13. The ODVA reaction of α-branched enals with isatins.

1.2.2 ODVA reaction of cyclic dienes

In the case of *α*,*β*-unsaturated carbonyl compounds such as esters and amides, the direct *γ*-deprotonation with mild organic bases is challenging due to the low acidity of the *γ*-hydrogen atoms. However, the corresponding cyclic derivatives (2(5*H*)-furanones) are readily deprotonated at the *γ*-position, since this generates the corresponding furanolates. As a result, there are several ODVA reactions reported using butenolides as nucleophiles.

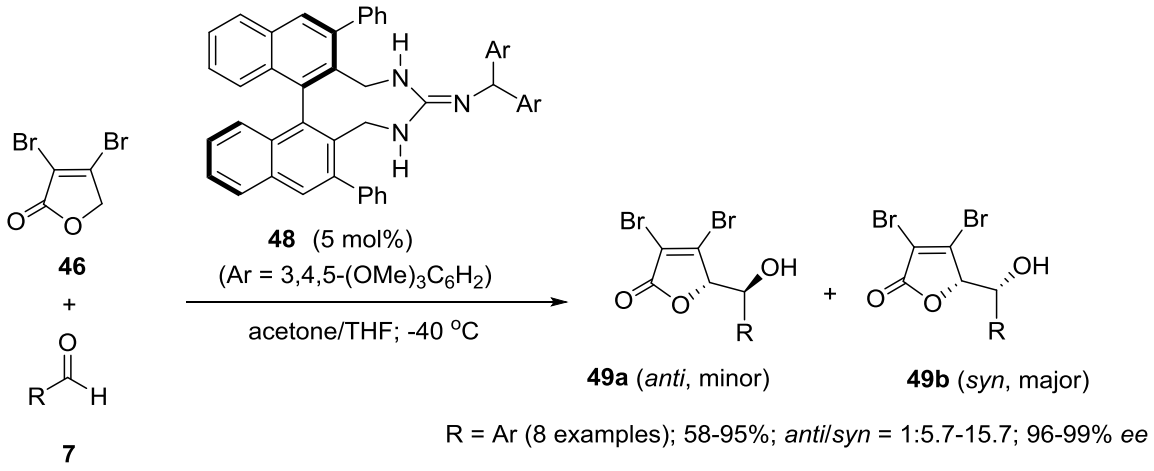
The first example of an ODVA of unsbstituted butenolide was reported by Bhat and co-workers.[21] A few aromatic aldehydes were tested using stoichiometric amounts of DABCO to obtain the vinylogous aldol adduct. Subsequently, Zhang *et al.*[22] examined the vinylogous aldol reaction of dihalofuranones **45** and **46** catalyzed by triethylamine (Scheme 1.14). Several aromatic and aliphatic aldehydes were examined and these reactions were found to be *syn* selective.



Scheme 1.14. The triethylamine catalyzed ODVA reactions of dihalofuranones.

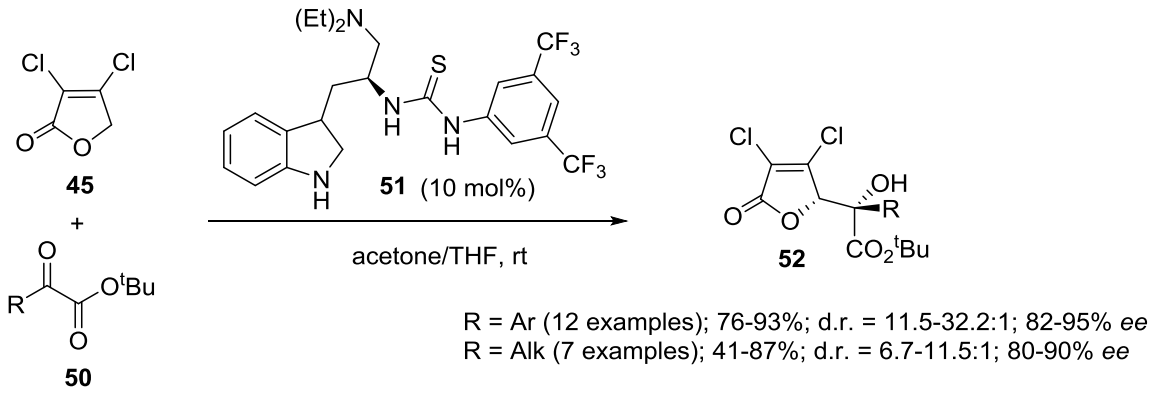
Terada and co-workers[23] developed a new class of chiral guanidines **48**, with an axially chiral binaphthyl backbone, as catalysts for the direct vinylogous aldol (DVA)

reaction. This was the first enantioselective DVA reaction of halogenated furanones **45** and **46**. Various types of aldehydes were examined to afford the major aldol adduct **49b**, with up to 99% *ee* (Scheme 1.15). It was also found that dibromofuranone **46** (X = Br) provides better diastereo- and enantioselectivity than the corresponding dichlorofuranone.



Scheme 1.15. The ODVA reaction catalyzed by chiral guanidine **48**.

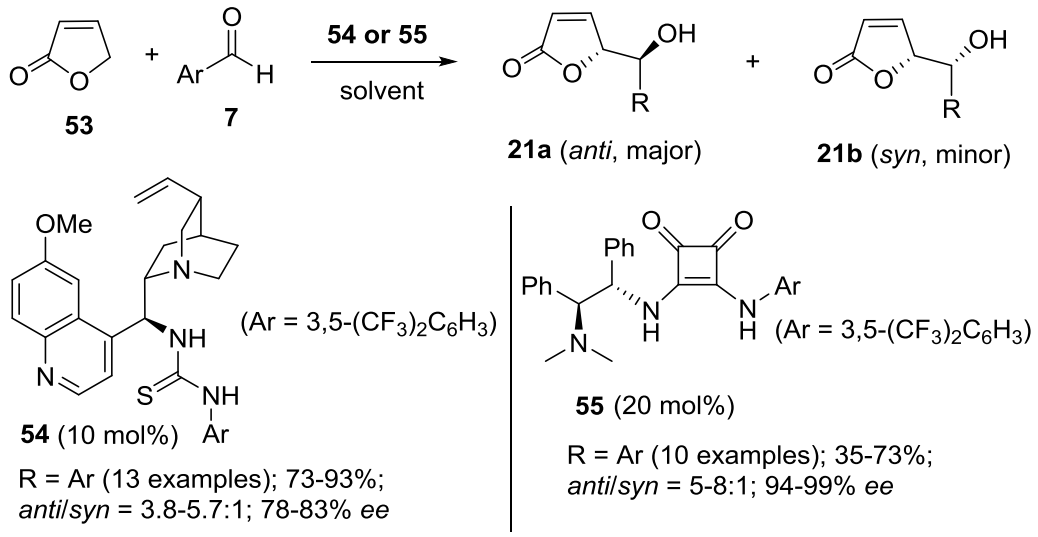
Recently, Lu *et al.*[24] reported the highly diastereo- and enantioselective direct vinylogous aldol reactions employing dichlorofuranone **45** and α-ketoesters **50** with the tryptophan-derived bifunctional organocatalyst **51** (Scheme 1.16). It was observed that aromatic aldehydes exhibit better stereoselection than their aliphatic counterparts. This method was also extended to the dibromofuranone **46**.



Scheme 1.16. The ODVA reaction catalyzed by tryptophan-derived thiourea catalyst.

It should be noted that the Terada guanidine catalysts (Scheme 1.15) are not applicable in reactions that employ the parent, unsubstituted *γ*-crotonolactone **53** as the nucleophile precursor, since the decomposition of **53** is significant in these reactions.[23] In addition, the tryptophan-derived catalyst used by Lu also required halofuranones as the nucleophile precursors (Scheme 1.16).

The first examples of ODVA reactions employing the unsubstitited *γ*-crotonolactone were reported by Feng and co-workers.[25] Several aminothiourea catalysts derived from diphenylethylenediamine, cyclohexanediamine and cinchona alkaloid based diamines were studied. Optimization studies revealed that the quinidine-derived aminothiourea **54** was the catalyst of choice when the reactions were carried out in diethyl ether at 30 ^{o}C (Scheme 1.17). Several aromatic aldehydes were used as substrates to provide the *anti* aldol adduct **21a** as the major product with a moderate diastereo- (3.8-5.7:1) and enantioselectivity (78-83% *ee*).

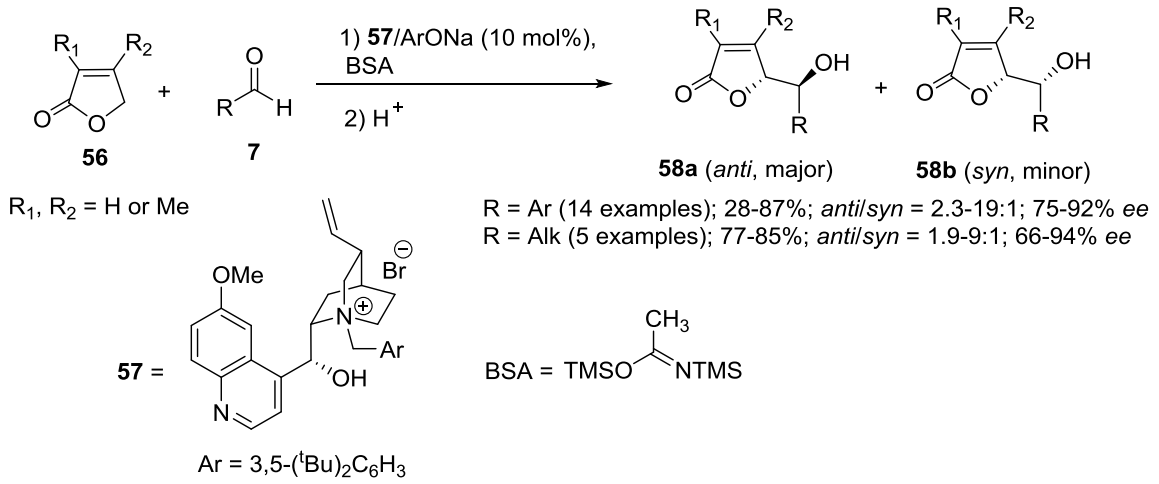


Scheme 1.17. The ODVA reaction catalyzed by thiourea and squaramide.

Simultaneous with the Feng study, the Pansare group[26] developed similar ODVA reactions of γ-crotonolactone with various aromatic aldehydes (Scheme 1.17). Among various thiourea and squaramide catalysts, the squaramide catalyst **55** gave the best result. Overall, good diastereoselectivities (5-8:1) and excellent enantioselectivities (94->99% *ee*) were obtained. Chapter 2 of this thesis discusses the details of the development of this method.

Very recently Levacher and Oudeyer[27] reported an *anti* selective ODVA reaction of (5*H*)-furan-2-one **56** with aldehydes (Scheme 1.18). The *in situ* generated chiral ammonium amide obtained from the chiral ammonium aryloxide and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) served as the catalyst. In general, the diastereoselectivities and enantioselectivities with the aromatic aldehydes (d.r. = 2.3-

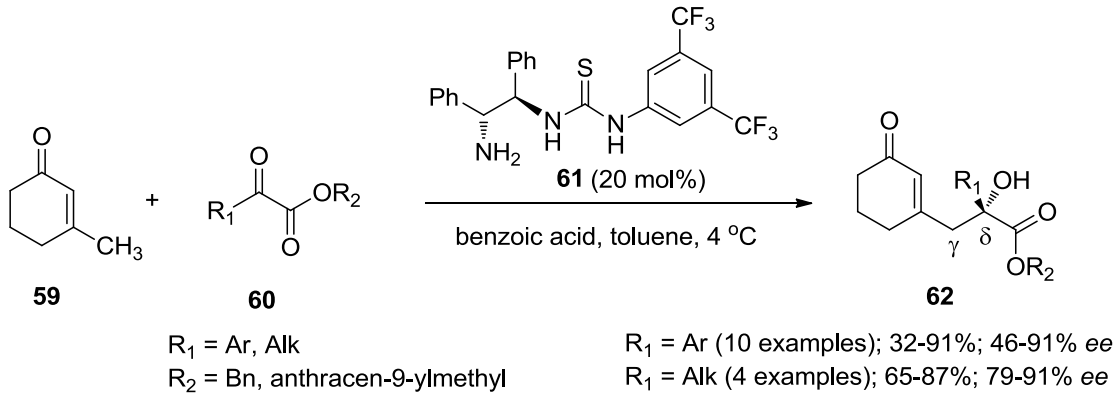
19:1; 75-92% *ee*), as well as the aliphatic aldehydes (d.r. = 1.9-9:1; 66-94% *ee*) were good.



Scheme 1.18. The ODVA reaction catalyzed by the combination of chiral quarternary ammonium aryloxide/*N*,*O*-bis(trimethylsilyl)acetamide.

In a recent report,[28] Melchiorre examined the ODVA reaction of 3-methyl-2-cyclohexen-1-one with various α-ketoesters (Scheme 1.19). Several aminothiourea catalysts derived from diphenylethylenediamine, cyclohexanediamine and cinchona alkaloid based diamines were studied. Optimization studies revealed that the diphenylethylenediamine-derived aminothiourea **61** was the catalyst of choice. Several aromatic as well as aliphatic aldehydes provided the aldol products with good enantioselectivity (46-91% *ee*). It should be noted that these reactions work only with the enone **59** as the nucleophile. Attempts to introduce two contiguous stereogenic centers (at the λ and δ positions) using differently β-substituted cyclohexenones have been

unsuccessful. Linear enones also proved to be unreactive under the reported reaction conditions.

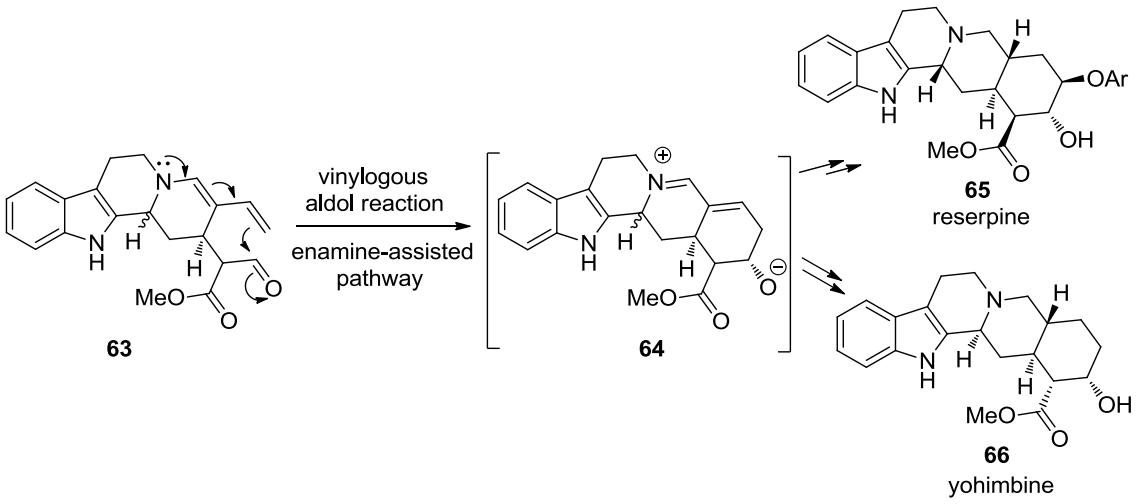


Scheme 1.19. The ODVA reaction catalyzed by primary amine thiourea.

1.3 Applications of ODVA reactions

One of the main focuses in modern organic chemistry is the development of efficient synthetic protocols that allow for the straightforward and economical construction of natural products with stereogenic complexity. The vinylogous aldol reaction uses α,β-unsaturated carbonyl substrates to construct δ-hydroxylated α,β-unsaturated carbonyls. These functional arrays are common structural motifs in the synthesis of enantiomerically pure biologically relevant natural products, especially those of polyketide origin.[2a] This has provided the impetus for developing highly stereoselective, catalytic vinylogous aldol reactions. Owing to the growing interest in OVMA reactions, much effort has been directed towards their direct application in the total synthesis of natural products to demonstrate their utility.[3a]

In nature, vinylogous aldol reactions are used in the construction of complex architectures in the forms of alkaloids or diterpenoids. For example, the proposed biogenetic pathways to the pentacyclic natural products reserpine **65** and yohimbine **66** skeletons involve enamine mediated vinylogous aldol reactions. The tetracyclic indole **63** can undergo an enamine assisted vinylogous aldol reaction leading to intermediate **64**, which undergoes functional group transformations to yield the products reserpine **65** and yohimbine **66** (Scheme 1.20).[29]



Scheme 1.20. A proposed biogenetic route to reserpine **65** and yohimbine **66**.

The organocatalytic, asymmetric vinylogous aldol reaction of 2-furanone is of interest because the reaction provides direct access to substituted γ-butenolides, an important structural motif in several natural products and biologically active compounds. γ-Butenolide derivatives are potential intermediates for the synthesis of enantiomerically pure, functionalized piperidine and tetrahydropyran derivatives.

The ODVA reaction of γ-crotonolactone with aldehydes can be used for the synthesis of substance P receptor antagonists (+)-L-733,060 and (+)-CP-99,994, which have been associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission. This methodology is also useful for the synthesis of 3-hydroxypipecolic acid, which is a component of tetrazomine, an antitumor agent and an antibiotic. The results of this work are described in Chapter 3.

Chapter 4 will describe a total synthesis of the antimalarial alkaloid (+)-febrifugine and a formal synthesis of (+)-halofuginone, an antimalarial agent, by employing the organocatalytic direct vinylogous aldol reaction.

This is a publication-based dissertation. As such, each subsequent Chapter is a slightly modified version of the publication cited at the beginning of each Chapter. The contributions of all authors are explained at the beginning of each Chapter.

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CHAPTER 2

Organocatalytic Asymmetric Direct Vinylogous Aldol Reactions of *γ*-Crotonolactone with Aromatic Aldehydes

This Chapter is based on the following publication:

Pansare, S. V.; Paul, E. K. *Chem. Commun.* **2011,** *47*, 1027-1029.

Contributions of authors

S. V. Pansare: research supervisor, manuscript preparation.

E. K. Paul: experimental work, manuscript preparation.

2.1 Introduction

The functionalized γ-butenolide (2(5*H*)-furanone) motif is found in several natural products and the synthesis of butenolides has therefore attracted considerable interest in recent years.[1] A popular approach to 5-substituted furanones involves the vinylogous Mukaiyama aldol reaction of silyloxyfurans[2] (Figure 2.1), and a number of asymmetric modifications of this reaction are known.[2f-n] In contrast, the alternative approach involving a direct vinylogous aldol reaction of furanones is less explored,[3] and asymmetric variants of this reaction employing chiral guanidine, aminothiourea and chiral ammonium amide as catalysts are reported.[4] A detailed account of these studies is provided in Chapter 1.

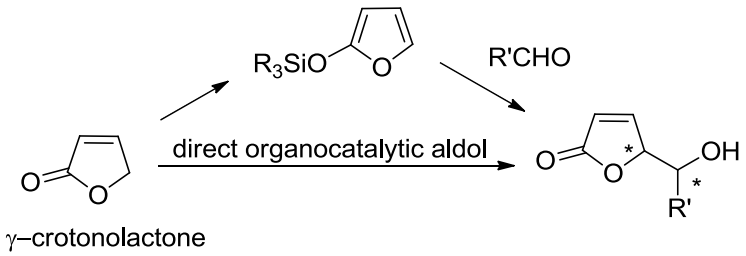


Figure 2.1. Direct aldol approach to butenolides.

The chiral guanidine-based system[4a] requires halolactones, and fails when crotonolactone is used as the substrate. The aminothiourea mediated reaction requires a fourfold excess of the nucleophile[4b] and there is scope for improvement of the stereoselectivity.[4b,c] Evidently, a catalytic system that addresses these issues would be desirable. The following sections describe our findings on the asymmetric, direct

vinylogous aldol reaction of crotonolactone with aromatic aldehydes mediated by aminothiourea and aminosquaramide catalysts.

2.2 Results and Discussions

We initially examined several classes of bifunctional, amine catalysts for the direct aldol reaction of crotonolactone: (a) cyclohexanediamine,[5a] diphenylethylenediamine,[5b] cinchonidine[5c,d] and cinchonine[5e,f] derived thioureas (**1, 2, 3** and **4**), (b) cyclohexanediamine and diphenylethylenediamine derived squaramides (**5, 6**)[5g-i] and (c) a proline-derived thiourea catalyst (**7**, Figure 2.2).

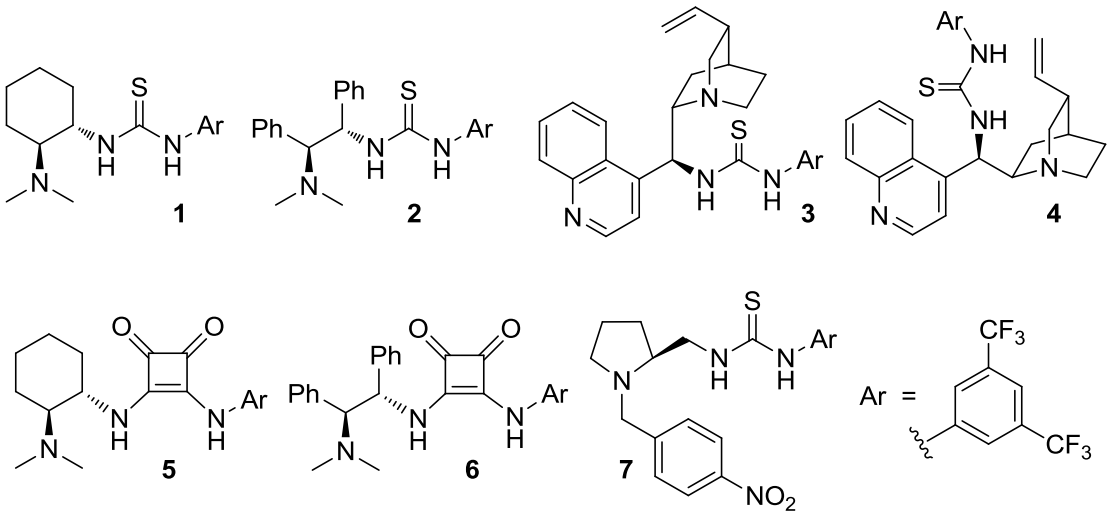
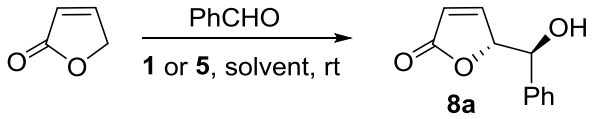


Figure 2.2. Bifunctional catalysts examined for the direct vinylogous aldol reaction of crotonolactone.

Orienting experiments were conducted with crotonolactone and benzaldehyde. Initially, the aldol reaction was examined with catalysts **1** and **5** in a variety of

solvents (Table 2.1).



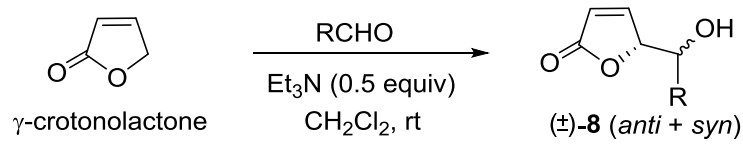
Entry[a]	Cat[b]	Solvent	t/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)
1	**1**	CH_2Cl_2	84	65	3.0/1	79
2	**1**	THF	84	78	5.8/1	76
3	**1**	toluene	84	89	1.0/1	78
4	**1**	EtOAc	84	72	3.2/1	72
5	**1**	$CHCl_3$	84	78	3.0/1	70
6	**1**	MeOH	84	81	2.6/1	40
7	**1**	DMF	84	63	3.6/1	45
8	**5**	CH_2Cl_2	12	88	2.0/1	49
9	**5**	THF	12	89	2.6/1	67
10	**5**	CH_2Cl_2[e]	168	76	5.3/1	94
11	**5**	THF[e]	168	92	5.0/1	90
12	**5**	$CHCl_3$[e]	168	98	5.9/1	91
13	**5**	toluene[e]	168	46	6.7/1	93
14	**5**	EtOAc[e]	168	32	5.6/1	96
15	**5**	DMF[e]	168	65	3.3/1	89
16	**5**	CH_3CN[e]	168	35	4.5/1	93

[a] 2 equiv. of crotonolactone. [b] 20 mol%. [c] Determined by ^{1}H NMR analysis of crude products. [d] Chiral HPLC analysis. [e] Reaction at 0 ^{o}C.

Table 2.1. Solvent survey for the vinylogous aldol reaction of crotonolactone.

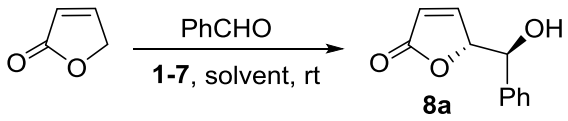
The reaction proceeded smoothly in most of the solvents examined (Table 2.1), and the expected aldol product **8a** was obtained as a mixture of *anti* and *syn* diastereomers, with the *anti* product predominating. Stereochemical assignments are based on the reported ^{1}H NMR data and the trend in chemical shifts for the *syn* and *anti* diastereomers of **8**.[2c] Overall, catalyst **1** provided moderate to good enantioselectivities for the *anti* product, except in methanol and DMF (entries 6 and 7, Table 2.1). Dichloromethane, THF and toluene emerged as promising solvents, when catalyst **1** was used, in terms of enantioselectivity, but the complete lack of diastereoselectivity in toluene precluded further studies in this solvent (entry 3, Table 2.1). At room temperature, **5** provided the aldol product **8a** with poor enantio- and diastereoselectivities in dichloromethane and THF as solvents (entries 8 and 9, Table 2.1). Much better results were obtained with **5** at 0 ^{o}C (entries 10-16, Table 2.1). Overall, good diastereoselectivities (3.3-6.7:1) and excellent enantioselectivities (89-96% *ee*) were obtained in most of the solvents for catalyst **5** at 0 ^{o}C. Low yields were obtained in ethyl acetate (32%) and acetonitrile (35%) (entries 14 and 16, Table 2.1), as solvents. From these studies, dichloromethane and THF emerged as promising solvents for further investigations.

The enantiomeric excess of **8a-l** was determined by chiral HPLC comparison with racemic samples. The racemic products in this study were prepared by adapting the triethylamine catalyzed reaction of dihalofuranones with aldehydes (Scheme 2.1).[3a]



Scheme 2.1. The triethylamine catalyzed reaction of γ-crotonolactone with aldehydes.

Subsequent studies, aimed at identifying the optimal catalyst, were therefore conducted in dichloromethane and THF. The results obtained from the catalyst survey are summarized in Table 2.2. The diphenylethylenediamine-thiourea catalyst (**2**) provided **8a** in relatively low yield and moderate enantioselectivity. In comparison, the cinchonidine and cinchonine based catalysts (**3** and **4**, respectively) generated **8a** in excellent yields, but the stereoselectivity was low (de: 1.8-4.8/1, *ee*: 50-71%). Much better results were obtained with the squaramide catalyst **5** in dichloromethane and THF at 0 ^{o}C (Table 2.2, entries 9 and 10, 94 and 91% *ee*). In comparison, the diphenylethylenediamine squaramide catalyst **6** was superior to **5** (Table 2.2, entries 11 and 12, 97 and 96% *ee*). At ambient temperature, **6** provided **8a** in excellent enantiomeric excess (97% *ee*) and good diastereoselectivity (7/1) in dichloromethane. Thus, two optimal catalytic systems, providing the *anti* diastereomer in greater than 90% *ee*, were identified from the catalyst and solvent survey, namely (a) the cyclohexanediamine squaramide catalyst **5** in dichloromethane at 0 ^{o}C (entry 9) and (b) the diphenylethylenediamine squaramide catalyst **6** in dichloromethane at ambient temperature (entry 11, Table 2.2).



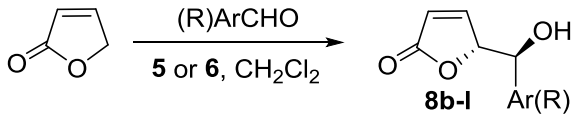
Entry[a]	Cat[b]	Solvent	T/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)
1	**1**	CH_2Cl_2	84	65	3/1	79
2	**1**	THF	84	78	5.8/1	76
3	**2**	CH_2Cl_2	96	32	6.7/1	77
4	**2**	THF	84	33	10/1	75
5	**3**	CH_2Cl_2	24	95	3.7/1	64
6	**3**	THF	48	95	2/1	50
7	**4**	CH_2Cl_2	24	98	1.8/1	65[e]
8	**4**	THF	48	95	4.8/1	71[e]
9	**5**	CH_2Cl_2[f]	168	76	5.3/1	94
10	**5**	THF[f]	84	46	4.3/1	91
11	**6**	CH_2Cl_2	120	35	7/1	97
12	**6**	THF	120	31	7/1	96
13	**7**	CH_2Cl_2	144	24	3.6/1	14
14	**7**	THF	144	25	4.5/1	14

[a] 2 equiv. of crotonolactone. [b] 20 mol%. [c] Determined by ^{1}H NMR analysis of crude products. [d] Chiral HPLC analysis. [e] enantiomeric product. [f] Reaction at 0 ^{o}C

Table 2.2. Catalyst survey for the vinylogous aldol reaction of crotonolactone.

The optimized conditions were employed in a study of the scope of the reaction with a variety of aldehydes. These investigations indicated that the choice of

catalyst **5** or **6** is determined by the nature of the aldehyde, and high enantioselectivities are obtained by proper pairing of the catalyst and aldehyde. Nonetheless, for most of the reactions, the diphenylethylenediamine derived catalyst **6** provided higher enantioselectivities than **5**. All isomers of methoxybenzaldehyde (entries 3-5, Table 2.3) provide high enantioselectivity. The diastereoselectivity for all of the reactions is moderate.[7] Overall, the level of stereoselection (average dr = 6/1, average *ee* = 94%) is higher than that obtained with cinchona alkaloid-thiourea catalysts.[4b] The aldol products **8a-l** exhibited spectral data in agreement with literature reports.[2,4] The results of these studies are summarized in Table 2.3.



Entry[a]	8	R	Cat[b]	Yield (%)[c]	dr[d] *(anti/syn)*	ee[e]% *anti (syn)*
1	b	4-MeC_6H_4	6	51	8/1	95 (32)
2	c	4-BrC_6H_4	6	62	8/1	95 (55)
3	d	4-$MeOC_6H_4$	6	35	8/1	97 (48)
4	e	2-$MeOC_6H_4$	6	58	8/1	96 (84)
5	f	3-$MeOC_6H_4$	6	54	6/1	96 (72)
6	g	4-ClC_6H_4	5	50	6/1	94 (83)
7	h	4-$NO_2C_6H_4$	6	50	5/1	>99 (50)
8	i	4-$CF_3C_6H_4$	6	60	6/1	95 (nd)
9	j	2-Naphthyl	6	73	6/1	95 (>99)
10	k	Cyclohexyl	5	50	3/1	>99 (>99)
11	l	1-Naphthyl	6	68	2/1	77 (80)

[a] 2 equiv of crotonolactone; [b] 20 mol%. [c] 144 h at 0 °C for **5** and 240 h at rt for **6**; [d] ^1H NMR of crude products. [e] Chiral HPLC analysis.

Table 2.3. Vinylogous aldol reaction of crotonolactone with various aldehydes.

The stereochemical outcome of the reaction is presumably governed by hydrogen bonding[8] of the aldehyde with the squaramide[5g-j] functionality and an ionic interaction of the deprotonated nucleophile and the resultant ammonium group in the catalyst (Figure 2.3). We have observed that the triethylamine catalyzed reaction of

crotonolactone with aldehydes (used for the preparation of racemic products in this study) has an intrinsic preference for the *anti* diastereomer (dr = ~2/1). The present results suggest that the hydrogen bonding functionality in the catalyst enhances this diastereoselectivity.

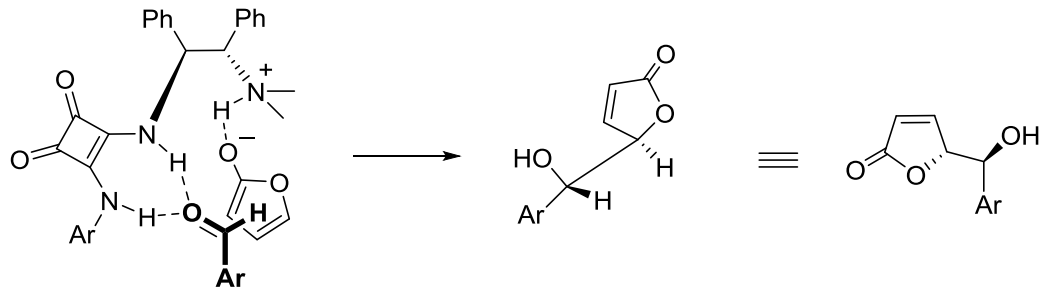
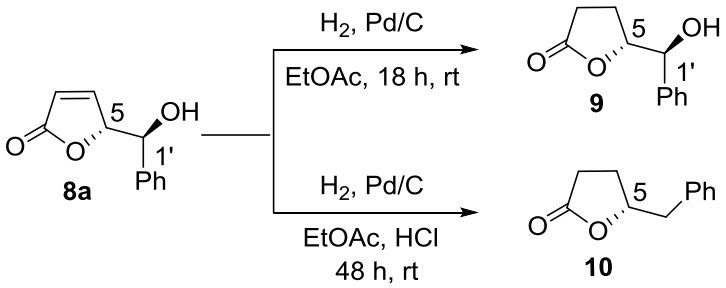


Figure 2.3. A proposed transition state assembly for the ODVA reaction leading to the *anti* aldol product.

2.2.1 Determination of the absolute configuration of 8a

Hydrogenation (Pd/C) of aldol product **8a** in ethyl acetate provided **9** (Scheme 2.2) which was dextrorotatory ($[\alpha]^{23}_{D}$ = +50.7 (*c* = 1.0, $CHCl_3$), 88% *ee*). The positive rotation indicates that lactone **9** is enantiomeric to the previously reported[2g] (5*S*,1'*R*) isomer ($[\alpha]^{25}_{D}$ = -53.3 (*c* = 0.22, $CHCl_3$) for **9** with 92% *ee*). Hydrogenation of **8a** in the presence of HCl, by adaptation of the literature procedure,[4a] provided **10** (Scheme 2.2) which was assigned the *R* configuration on the basis of chiral HPLC retention times[7] (Chiralcel OD-H, hexanes/2-propanol 80/20, 1 mL/min, 214 nm, t_S = 5.95 min, t_R = 6.74

min). Lactone **9** is therefore assigned the (5*R*,1'*S*) configuration, and compounds **8a-l** are also assigned the (5*R*,1'*S*) configuration by analogy.



Scheme 2.2. Hydrogenation and hydrogenolysis of aldol product.

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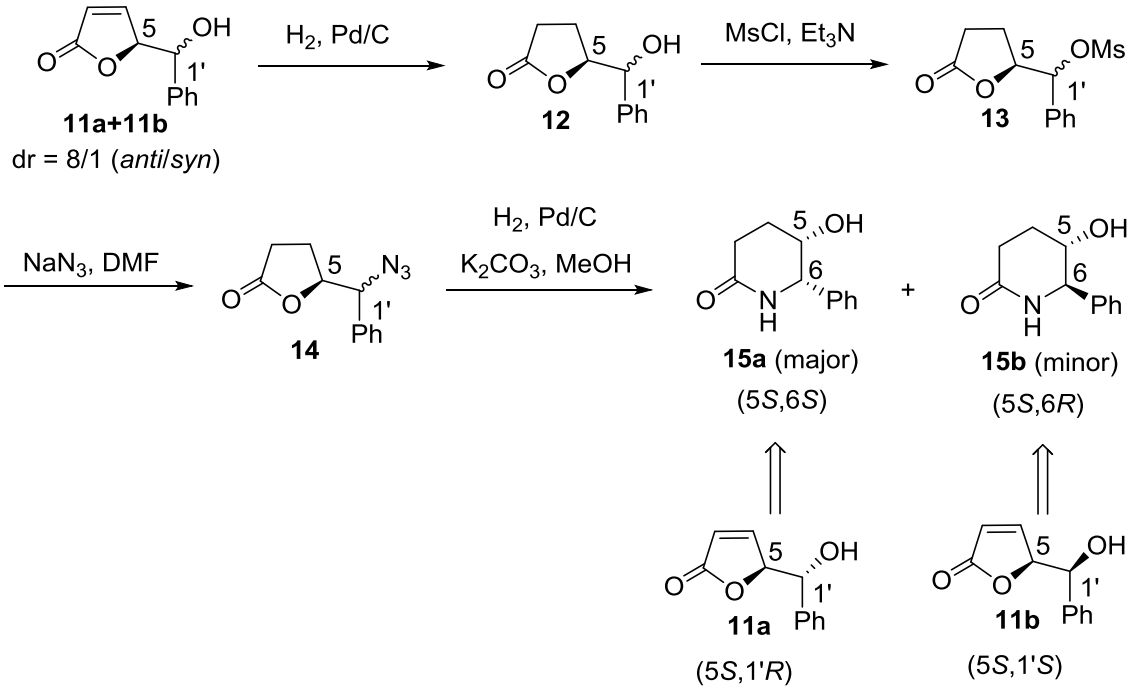
It was also shown that the aldol products **11a** and **11b** are diastereomeric at C-1', and not at C-5, by converting the aldol products **11a** and **11b** into lactam **15a** and **15b** via a series of simple transformations (Scheme 2.3). Hydrogenation of **11** (8/1 mixture of **11a**/**11b**) to the butyrolactone **12**, subsequent mesylation of the secondary alcohol to give **13** and displacement of the mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **14**. Reduction of the azide (H_2, Pd/C), in the presence of a base (K_2CO_3), generated the required piperidones **15a** and **15b**. At this stage, **15a** (*cis* isomer) was easily separated from the minor **15b** (*trans* isomer) by flash column chromatography. The optical rotation of **15a** (*cis* isomer) was consistent with that reported for the (5*S*,6*S*) isomer in the literature ($[\alpha]_D^{23}$ = +55.3 (*c* = 1.1, CH_2Cl_2), 97% *ee*; lit. $[\alpha]_D^{25}$ = +52.0 (*c* = 1.1, CH_2Cl_2),[8] for a 99% *ee* sample). The optical rotation of the **15b** (*trans* isomer) was opposite to that reported for the (5*R*,6*S*) isomer in the literature ($[\alpha]_D^{23}$ = +26.0 (*c* 1.0 , MeOH), 96% *ee*; lit. $[\alpha]_D^{20}$ = –25.9 (*c* = 0.27, MeOH),[9] for a 92% *ee* sample). Therefore, **15b** is assigned the (5*S*,6*R*) absolute configuration. These

observations indicate that **15b** is obtained from the (5*S*,1'*S*) isomer of **11b** which is diastereomeric to **11a** at C-1'. The aldol reaction therefore generates aldol products which are diastereomeric at the secondary alcohol stereocenter.



Scheme 2.3. Conversion of aldol product into lactam.

2.3 Conclusions

In conclusion, a highly enantioselective, catalytic aldol reaction of crotonolactone with aldehydes was developed. A notable outcome of this study is the superior performance of the squaramide catalysts over the conventional aminothiourea catalysts.

2.4 Experimental section

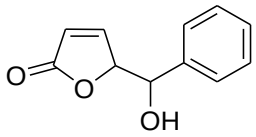
General: All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

General Procedure for the organocatalytic direct vinylogous aldol reaction:

To the catalyst (0.10 mmol, in a 2.0 mL Reacti-Vial™ or a standard 3.0 mL vial) was added the aldehyde (0.50 mmol) followed by γ-crotonolactone (2-(5*H*)-furanone) (1.0 mmol) and dichloromethane (0.50 mL). The suspension was stirred for 10 d at room temperature (for catalyst **6**) or kept for 7 d at 0 ^{o}C with occassional shaking (for catalyst **5**). The mixture was then diluted with ethyl acetate (1.0 mL) and aqueous HCl (2 N) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1). The diastereomeric composition (*anti*/*syn*) was determined by ^{1}H NMR analysis of the crude product. The enantiomeric excess was determined by HPLC (Chiralpak AD-H or AS-H column, flow

rate 1.0 mL/min, UV detection at 210 or 254 nm) by comparison with reported retention times[4b] for compounds **8a-l,** and also by comparison with racemic standards (prepared by using triethylamine as the catalyst) for compounds **8h, 8i** and **8l**. The absolute configuration of **8a** was assigned by correlation. Absolute configurations of **8b-l** are assigned by analogy within the series.

5-[Hydroxy(phenyl)methyl]furan-2(5*H*)-one (8a):

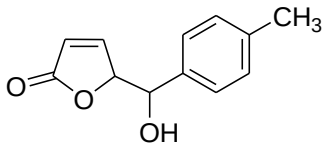


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with benzaldehyde (53 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 34 mg (35%) of **8a** as a white solid.

IR: 3432, 1728, 1167, 1039, 820 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.43-7.34 (m, 6H, Ar*H* and COCH=C*H*), 6.19 (dd, 1H, *J* = 5.8, 1.9 Hz, COC*H*=CH), 5.19-5.18 (br m, 1H, CH=CHC*H*), 5.09 (br t, 1H, *J* = 4.1 Hz, ArC*H*OH), 2.25 (d, 1H, *J* = 3.8 Hz, O*H*); ***Syn* diastereomer:** δ 7.42-7.36 (m, 5H, Ar*H*), 7.17 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.13 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.17 (apparent dt, 1H, *J* = 7.0, 1.5 Hz, CH=CHC*H*), 4.71 (d, 1H, *J* = 7.0 Hz, ArC*H*OH), 2.78 (s, 1H, O*H*); MS (APCI pos.): *m/z* 191.0 (M+1).

HPLC: Chiralpak AS-H, hexanes/2-propanol 90/10, 254 nm, t_1 = 27.8 min (major *anti*), t_2 = 36.2 min, (*syn*), t_3 = 49.6 min (*syn*), t_4 = 66.8 min (minor *anti*). Ee: 97% (*anti*).

5-[Hydroxy(*p*-tolyl)methyl]furan-2(5*H*)-one (8b):

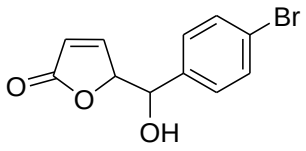


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 4-methylbenzaldehyde (59 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 52 mg (51%) of **8b** as a white solid.

IR: 3401, 1736, 1325, 1170, 1102, 1079, 1039, 917, 877 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.36 (dd, 1H, *J* = 5.8, 1.4 Hz, COCH=C*H*), 7.28 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.22 (d, 2H, *J* = 8.0 Hz, Ar*H*, ortho to CH_3), 6.18 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.17-5.15 (m, 1H, CH=CHC*H*), 5.04 (br t, 1H, *J* = 4.0 Hz, ArC*H*OH), 2.37 (3H, CH_3), 2.22 (d, 1H, *J* = 4.0 Hz, O*H*), 2.37 (3H, CH_3); ***Syn* diastereomer:** δ 7.28 (d, 2H, *J*= 8.0 Hz, Ar*H*), 7.22 (d, 2H, *J* = 8.0 Hz, ortho to CH_3), 7.16 (dd, 1H, *J* = 5.8, 1.6 Hz, COCH=C*H*), 6.13 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.15-5.17 (m, 1H, CH=CHC*H*), 4.66 (dd, 1H, *J* = 6.9, 3.0 Hz, ArC*H*OH), 2.58 (d, 1H, *J* = 3.0 Hz, O*H*), 2.37 (3H, CH_3); MS (APCI pos.): *m/z* 205.0 (M+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 254 nm, t_1 = 20.0 min (major *anti*), t_2 = 22.2 min, (minor *anti*), t_3 = 26.8 min (minor *syn*), t_4 = 29.0 min (major *syn*). Ee: 95% (*anti*).

5-[Hydroxy(4-bromophenyl)methyl]furan-2(5*H*)-one (8c):

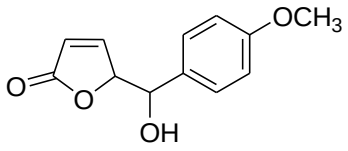


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 4-bromobenzaldehyde (93 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 83 mg (62%) of **8c** as a white solid.

IR: 3343, 1742, 1486, 1399, 1191, 1176, 1095, 1074, 1041, 1008, 917, 880, 831, 808 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.55 (d, 2H, *J* = 8.4 Hz, Ar*H*, ortho to Br), 7.32 (dd, 1H, *J* = 5.8, 1.4 Hz, COCH=C*H*), 7.29 (d, 2H, *J* = 8.5 Hz, Ar*H*), 6.19 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.15-5.13 (m, 1H, CH=CHC*H*), 5.04 (t, 1H, *J* = 4.0 Hz, ArC*H*OH), 2.48 (d, 1H, *J* = 4.0 Hz, O*H*); ***Syn* diastereomer:** δ 7.55 (d, 2H, *J* = 8.4 Hz, Ar*H*, ortho to Br), 7.29 (d, 2H, *J* = 8.4 Hz), 7.20 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.14 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.15-5.13 (m, 1H, CH=CHC*H*), 4.73 (dd, 1H, *J* = 6.7, 3.3 Hz, ArC*H*OH), 2.73 (d, 1H, *J* = 3.3 Hz, O*H*); MS (APCI pos.): *m/z* 269.1 (M^+).

HPLC: Chiralpak AD-H, hexanes/2-propanol 88/12, 254 nm, t_1 = 9.6 min (major *anti*), t_2 = 10.4 min (minor *syn*), t_3 = 10.8 min (minor *anti*), t_4 = 11.6 min (major *syn*). Ee: 95% (*anti*).

5-[Hydroxy(4-methoxyphenyl)methyl]furan-2(5*H*)-one (8d):

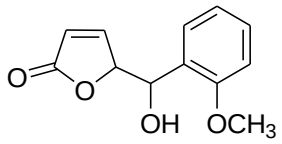


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 4-methoxybenzaldehyde (63 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 39 mg (35%) of **8d** as a white solid.

IR: 3357, 1742, 1585, 1510, 1242, 1171, 1101, 1085, 1029, 1008, 877, 827, 814 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.39 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 7.32 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.93 (d, 2H, *J* = 8.7 Hz, ortho to OCH_3), 6.18 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.15-5.14 (m, 1H, CH=CHC*H*), 5.0 (t, 1H, *J* = 4.0 Hz, ArC*H*OH), 3.82 (s, 3H, OCH_3), 2.26 (d, 1H, *J* = 4.0 Hz, O*H*); ***Syn* diastereomer:** δ 7.32 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.16 (dd, 1H, *J* = 5.8, 1.6 Hz, COCH=C*H*), 6.93 (d, 2H, *J* = 8.7 Hz, ortho to OCH_3), 6.13 (dd, 1H, *J* = 5.8, 2.1 Hz, COC*H*=CH), 5.15-5.14 (m, 1H, CH=CHC*H*), 4.65 (dd, 1H, *J* = 7.1, 3.0 Hz, ArC*H*OH), 3.82 (s, 3H, OCH_3), 2.61 (d, 1H, *J* = 3.0 Hz, O*H*); MS (APCI pos.): *m/z* 221.0 (M+1), 203.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 90/10, 254 nm, t_1 = 15.1 min (major *anti*), t_2 = 17.7 min, (minor *anti*), t_3 = 19.0 min (minor *syn*), t_4 = 20.7 min (major *syn*). Ee: 97% (*anti*).

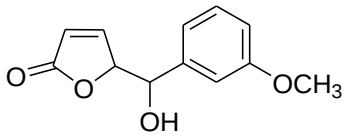
5-[Hydroxy(2-methoxyphenyl)methyl]furan-2(5*H*)-one (8e):



Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 2-methoxybenzaldehyde (63 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 64 mg (58%) of **8e** as a colorless liquid.

IR: 3418, 1733, 1601, 1491, 1462, 1238, 1160, 1095, 1036, 1022, 816 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.40 (dd, 1H, *J* = 5.8, 1.0, COCH=C*H*), 7.34-7.31 (m, 2H, Ar*H* ortho and para to OCH_3), 7.03 (t, 1 H, *J* = 7.5 Hz, Ar*H*, meta to OCH_3), 6.92 (d, 1H, *J* = 8.3, Ar*H*), 6.15 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.38-5.37 (m, 1H, CH=CHC*H*), 5.31 (t, 1H, *J* = 5.7 Hz, ArC*H*OH), 3.89 (s, 3H, OCH_3), 2.82 (d, 1H, *J* = 5.7 Hz, O*H*); ***Syn* diastereomer:** δ 7.34-7.31 (m, 2H, Ar*H* ortho and para to OCH_3), 7.18 (dd, 1H, *J* = 5.8, 1.1, COCH=C*H*), 7.03 (t, 1 H, *J* = 7.5 Hz, Ar*H*, meta to OCH_3), 6.92 (d, 1H, *J* = 8.3, Ar*H*), 6.12 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.24-5.23 (br dt, 1H, *J* = 6.6, 1.5, CH=CHC*H*) 5.02 (t, 1H, *J* = 5.7 Hz, ArC*H*OH), 3.85 (s, 3H, OCH_3), 3.06 (d, 1H, *J* = 5.7 Hz, O*H*); MS (APCI neg.): *m/z* 219 (M^+); APCI pos. m/z 203.0 ((M-H_2O)+1). HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254, t_1 = 8.4 min (major *anti*), t_2 = 11.0 min, (minor *anti*), t_3 = 12.9 min (major *syn*), t_4 = 16.3 min (minor *syn*). Ee: 96% (*anti*).

5-[Hydroxy(3-methoxyphenyl)methyl]furan-2(5*H*)-one (8f):

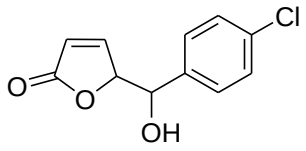


Reaction of *γ*-crotonolactone (70 µL, 1.0 mmol) with 3-methoxybenzaldehyde (63 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0. 10 mmol) according to the general procedure provided 60 mg (54%) of **8f** as a colorless liquid.

IR: 3420, 1735,1600, 1585, 1489, 1456, 1435, 1256, 1157, 1034, 825 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.35-7.29 (m, 2H, Ar*H*, COCH=C*H*), 6.97-6.87 (m, 3H, Ar*H*), 6.17 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.18-5.15 (m, 1H, CH=CHC*H*), 5.08 (t, 1H, *J* = 4.0 Hz, ArC*H*OH), 3.82 (s, 3H, OCH_3), 2.73(d, 1H, *J* = 4.0 Hz, O*H*); ***Syn* diastereomer:** δ 7.35-7.29 (m, 1H, Ar*H*), 7.18 (dd, 1H, *J* = 5.8, 1.4 Hz, COCH=C*H*), 6.97-6.87 (m, 3H, Ar*H*), 6.12 (dd, 1H, *J* = 5.8,1.9 Hz, COC*H*=CH), 5.18-5.15 (m, 1H, CH=CHC*H*), 4.68 (dd, 1H, *J* = 7.0, 3.1 Hz, ArC*H*OH), 3.82 (s, 3H, OCH_3), 2.94 (d, 1H, *J* = 3.1 Hz, O*H*); MS (APCI pos.): *m/z* 221.0 (M+1), 203.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 90/10, 210 nm, t_1 = 14.2 min (major *anti*), t_2 = 18.3 min, (minor *anti*), t_3 = 20.0 min (minor *syn*), t_4 = 21.4 min (major *syn*). Ee: 96% (*anti*).

5-[Hydroxy(4-chlorophenyl)methyl]furan-2(5*H*)-one (8g):

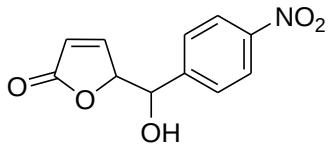


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 4-chlorobenzaldehyde (70 mg, 0.50 mmol) catalyzed by **5** (45 mg, 0.10 mmol) according to the general procedure provided 56 mg (50%) of **8g** as a white solid.

IR: 3420, 1732, 1491, 1175, 1093, 1078, 1042, 917, 852, 812 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.40-7.31 (m, 5H, Ar*H*, COCH=C*H*), 6.20 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.15-5.13 (m, 1H, CH=CHC*H*), 5.05 (t, 1H, *J* = 4.0 Hz, ArC*H*OH), 2.38 (d, 1H, *J* = 4.0 Hz, O*H*); ***Syn* diastereomer:** δ 7.40-7.31 (m, 4H, Ar*H*), 7.20 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.14 (dd, 1H, *J* = 5.8,2.0 Hz, COCH=C*H*), 5.15-5.13 (m, 1H, CH=CHC*H*), 4.74 (dd, 1H, *J* = 6.8, 3.2 Hz, ArC*H*OH), 2.67 (d, 1H, *J* = 3.2 Hz, O*H*); MS (APCI pos.): *m/z* 225.0 (M+1), 207.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H hexanes/2-propanol 95/5, 210 nm, t_1 = 21.1 min (major *anti*), t_2 = 24.2 min, (minor *anti*), t_3 = 25.9 min (major *syn*), t_4 = 29.4 min (minor *syn*). Ee: 94% (*anti*).

5-[Hydroxy(4-nitrophenyl)methyl]furan-2(5*H*)-one (8h):

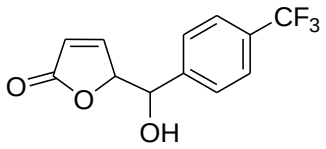


Reaction of γ-crotonolactone (70 µL, 1.0 mmol) with 4-nitrobenzaldehyde (76 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 59 mg (50%) of **8h** as a yellow solid.

IR: 3438, 1746, 1515, 1348, 1169, 1103, 1039, 916, 833 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 8.26 (d, 2H, *J* = 8.7 Hz, Ar*H*, ortho to NO_2), 7.63 (d, *J* = 8.7, 2H, Ar*H*), 7.30 (dd, 1H, *J* = 5.9,1.6 Hz, COCH=C*H*), 6.17 (dd, 1 H, *J* = 5.9, 1.8 Hz, COC*H*=CH), 5.21-5.19 (m, 2H, CH=CHC*H*, ArC*H*OH), 2.77 (d, 1H, *J* = 3.7 Hz, O*H*); ***Syn* diastereomer:** δ 8.29 (d, 2H, *J* = 8.7 Hz, Ar*H*, ortho to NO_2), 7.66-7.59 (m, 2H, Ar*H*), 7.21 (m, 1H, COCH=C*H*), 6.24 (dd, 1 H, *J* = 5.8, 1.4 Hz, COC*H*=CH), 5.0-4.98 (m, 2H, CH=CHC*H*, ArC*H*OH), 2.59 (d, 1H, *J* = 3.5 Hz, O*H*); MS (APCI pos.): *m/z* 236.1 (M+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 254 nm, t_1 = 52.4 min (major *anti*), t_2 = 59.1 min, (major *syn*), 70.5 (minor *syn*). Ee: >99% (*anti*).

5-[Hydroxy(4-trifluoromethylphenyl)methyl]furan-2(5*H*)-one (8i):

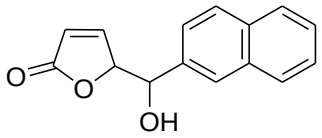


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 4-trifluoromethylbenzaldehyde (67 µL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 78 mg (60%) of **8i** as a colorless solid.

IR: 3413, 1739, 1322, 1161, 1100, 1065, 1040, 1016, 816 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.68 (d, 2H, *J* = 8.1 Ar*H*), 7.55 (d, 2H, *J* = 8.1, Ar*H*), 7.31 (dd, 1H, *J* = 5.8, 1.4 Hz, COCH=C*H*), 6.21 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.19-5.14 (m, 2H, CH=CHC*H*O, ArC*H*OH), 2.38 (d, 1H, *J* = 3.9 Hz, O*H*); ***Syn* diastereomer:** δ 7.68 (d, 2H, *J* = 5.7, Ar*H*), 7.55 (d, 2H, *J* = 5.7, Ar*H*), 7.24 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.15 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.19-5.14 (m, 1H, CH=CHC*H*), 4.91 (m, 1H, ArC*H*OH), 2.38 (d, 1H, *J* = 3.4 Hz, O*H*); MS (APCI pos.): *m/z* 259.2 (M+1), 241.1 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 97/3, 254 nm, t_1 = 28.9 min (major *anti*), t_2 = 32.4 min, (minor *anti*). Ee: 95% (*anti*).

5-[Hydroxy (naphthalen-2-yl)methyl]furan-2(5*H*)-one (8j):

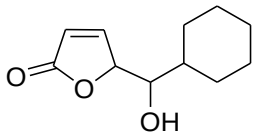


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 2-naphthaldehyde (78 mg, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 88 mg (73%) of **8j** as a pale yellow solid.

IR: 3359, 1752, 1731, 1172, 1077, 1041, 824 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.90-7.85 (m, 4H, Ar*H*), 7.53-7.50 (m, 3H, Ar*H*), 7.36 (dd, 1H, *J* = 5.8, 1.4 Hz COCH=C*H*), 6.19 (dd, 1 H, *J* = 5.8, 1.9 Hz, COC*H*=CH), 5.29-5.26 (m, 2H, CH=CHC*H*, ArC*H*OH), 2.51 (d, 1H, *J* = 3.7 Hz, O*H*); ***Syn* diastereomer:** δ 7.90-7.85 (m, 4H, Ar*H*), 7.53-7.50 (m, 3H, Ar*H*), 7.18 (dd, 1H, *J* = 5.8, 1.6 Hz, COCH=C*H*), 6.13 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.29-5.26 (m, 2H, CH=CHC*H*), 4.88 (dd, 1H, *J* = 7.1, 3.1 Hz, ArC*H*OH), 2.81 (d, 1H, *J* = 3.1 Hz, O*H*); MS (APCI pos.): *m/z* 241.0 (M+1), 223.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254 nm, t_1 = 9.5 min (major *anti*), t_2 = 11.8 min, (minor *anti*), t_3 = 12.6 min (major *syn*), t_4= 13.6 min (minor *syn*). Ee: 95% (*anti*).

5-[Hydroxy(cyclohexyl)methyl]furan-2(5*H*)-one (8k):

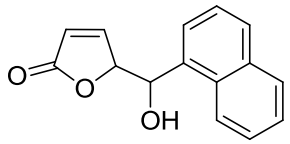


Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with cyclohexanecarboxaldehyde (60 μL, 0.50 mmol) catalyzed by **5** (45 mg, 0.10 mmol) according to the general procedure provided 49 mg (50%) of **8k** as a white solid.

IR: 3420, 1747, 1715, 1154, 1112, 1096, 1029, 1004, 870, 845 829 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.59 (dd, 1H, *J* = 5.8, 1.4 Hz, COCH=C*H*), 6.19 (dd, 1 H, *J* = 5.8, 1.9 Hz, COC*H*=CH), 5.10 (dt, 1H, *J* = 5.7, 1.6 Hz, CH=CHC*H*), 3.61 (apparent q, 1H, *J* = 5.6 Hz, ArC*H*OH), 1.98-1.96 (m, 1H, C*H*CH_2), 1.82-1.54 (m, 4H, CH_2), 1.33-1.10 (m, 6H, CH_2); ***Syn* diastereomer:** δ 7.45 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.19 (dd, 1H, *J* = 5.8, 1.9 Hz, COC*H*=CH), 5.18 (m, 1H, CH=CHC*H*), 3.49-3.45 (m, 1H, ArC*H*OH), 1.98-1.96 (m, 1H, C*H*CH_2), 1.82-1.54 (m, 4H, CH_2), 1.33-1.10 (m, 6H, CH_2); MS (APCI pos.): *m/z* 197.0 (M+1), 179.1 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 95/5, 210 nm, t_1= 15.4 min (major *anti*), t_2 = 17.5 min (major *syn*). Ee: >99% (*anti*).

5-[Hydroxy(naphthalen-1-yl)methyl]furan-2(5*H*)-one (8l):



Reaction of γ-crotonolactone (70 μL, 1.0 mmol) with 1-naphthaldehyde (68 μL, 0.50 mmol) catalyzed by **6** (55 mg, 0.10 mmol) according to the general procedure provided 82 mg (68%) of **8k** as a yellow solid.

IR: 3414, 1730, 1165, 1102, 1081, 1042, 882, 823, 797, 775 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 8.02 (d, 1H, *J* = 8.5 Hz, Ar*H*), 7.93 (d, 1H, *J* = 7.6 Hz, Ar*H*), 7.88 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.74 (d, 1H, *J* = 7.2 Hz, Ar*H*), 7.59-7.53 (m, 3H, Ar*H* & COCH=C*H*), 7.27-7.25 (m, 1H, Ar*H*), 6.20 (dd, 1 H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.98 (t, 1H, *J* = 3.5 Hz, CH=CHC*H*), 5.44-5.43 (m, 1H, ArC*H*OH), 2.57 (d, 1H, *J* = 3.8 Hz, O*H*); ***Syn* diastereomer:** δ 7.98 (m, 1H, Ar*H*), 7.88-7.87 (m, 2H, Ar*H*), 7.74 (d, 1H, *J* = 7.0 Hz, Ar*H*), 7.59-7.53 (m, 3H, Ar*H* & COCH=C*H*), 7.27-7.25 (m, 1H, Ar*H*), 6.95 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.14 (dd, 1H, *J* = 5.8, 2.0 Hz, COC*H*=CH), 5.46-5.45 (m, 1H, CH=CHC*H*), 5.39 (dt, 1H, *J* = 3.4, 1.6 Hz, ArC*H*OH), 2.92 (d, 1H, *J* = 3.2 Hz, O*H*); MS (APCI pos.): *m/z* 241.0 (M+1), 223.0 ((M-H_2O)+1).

HPLC: Chiralpak AD-H, hexanes/2-propanol 85/15, 254 nm, t_1= 8.7 min (major *anti*), t_2 = 9.5 min (minor *anti*), t_3 = 13.8 min (major *syn*), t_4= 17.3 min (minor *syn*). Ee: 77% (*anti*).

2.5 References:

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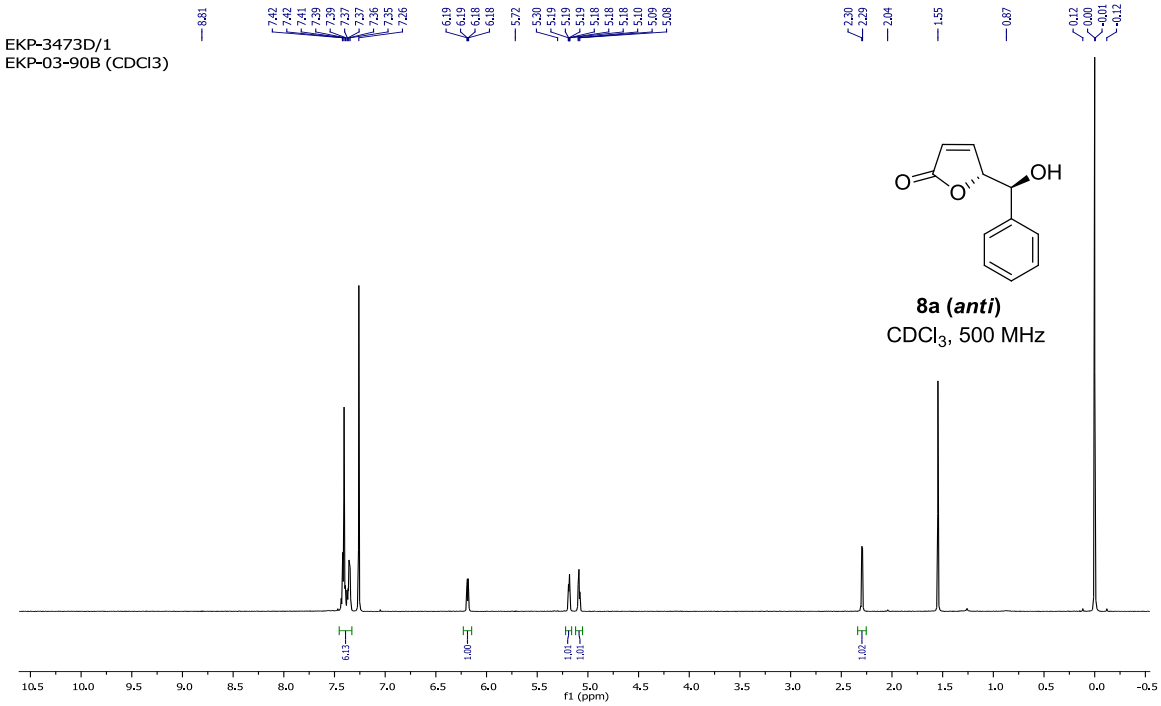
2.6 Selected ^{1}H NMR spectra

EKP-3473D/1
EKP-03-90B (CDCl3)



8a (*anti*)
$CDCl_3$, 500 MHz

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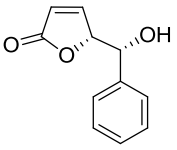

8a (*syn*)
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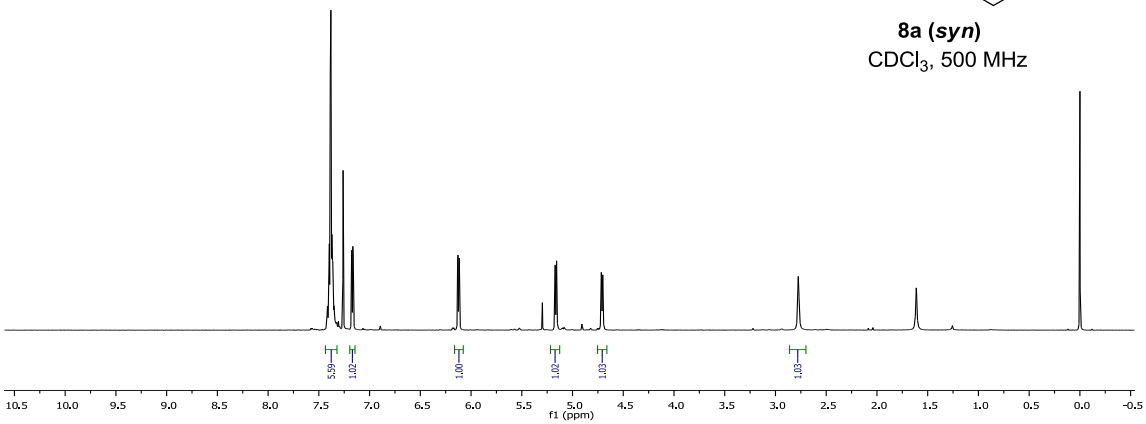

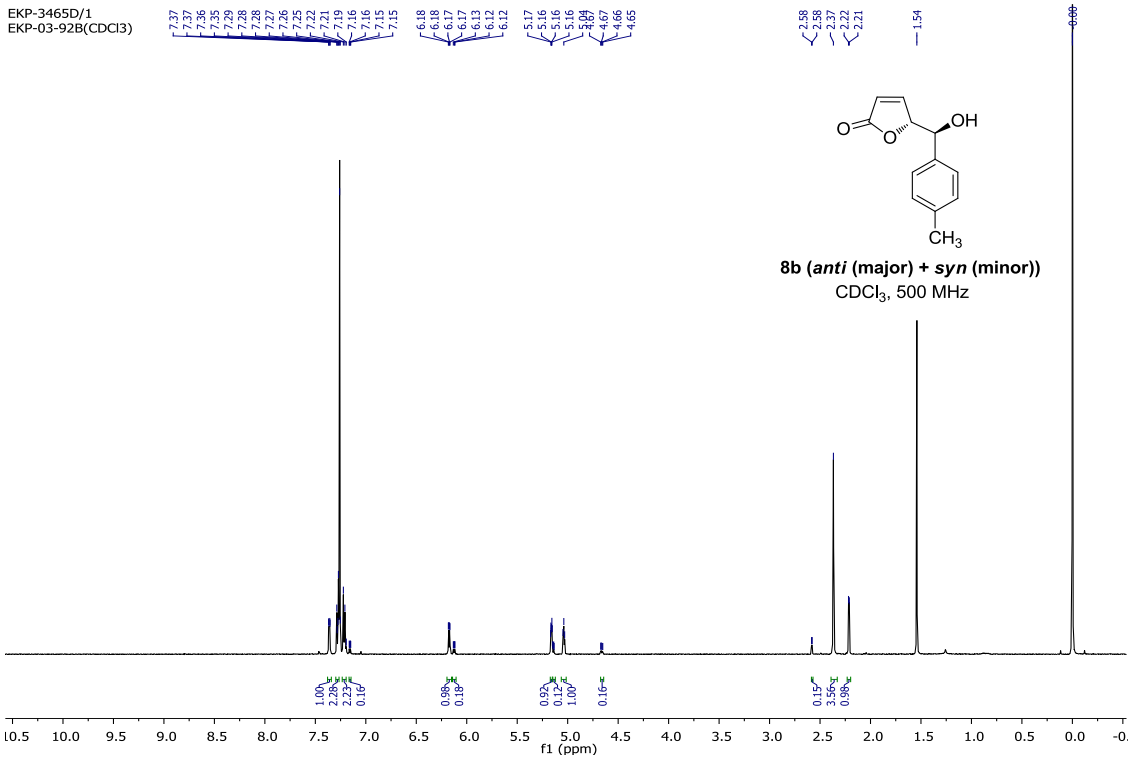
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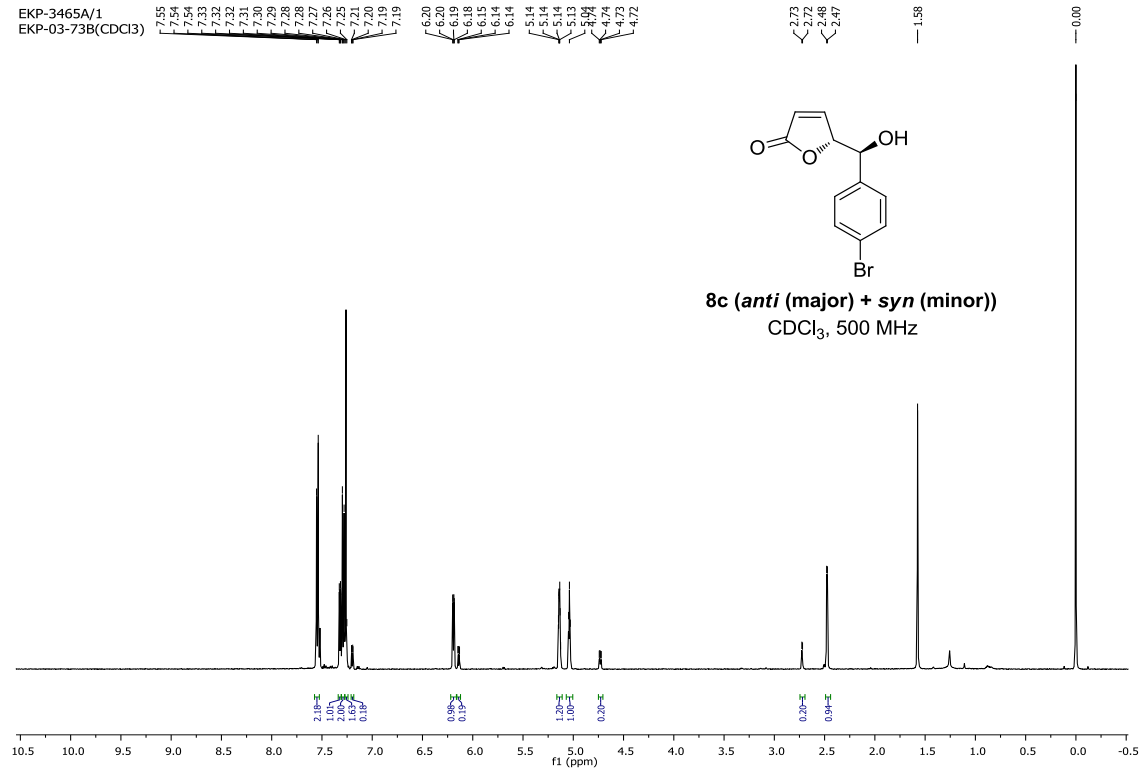
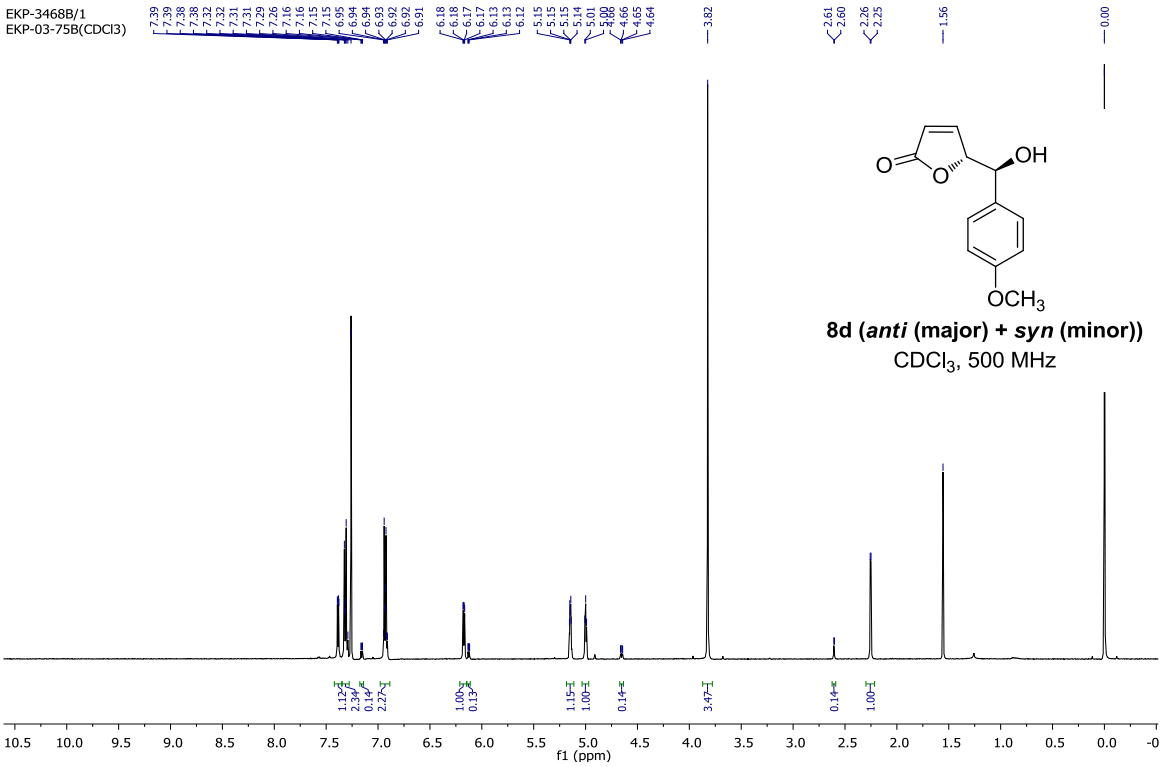
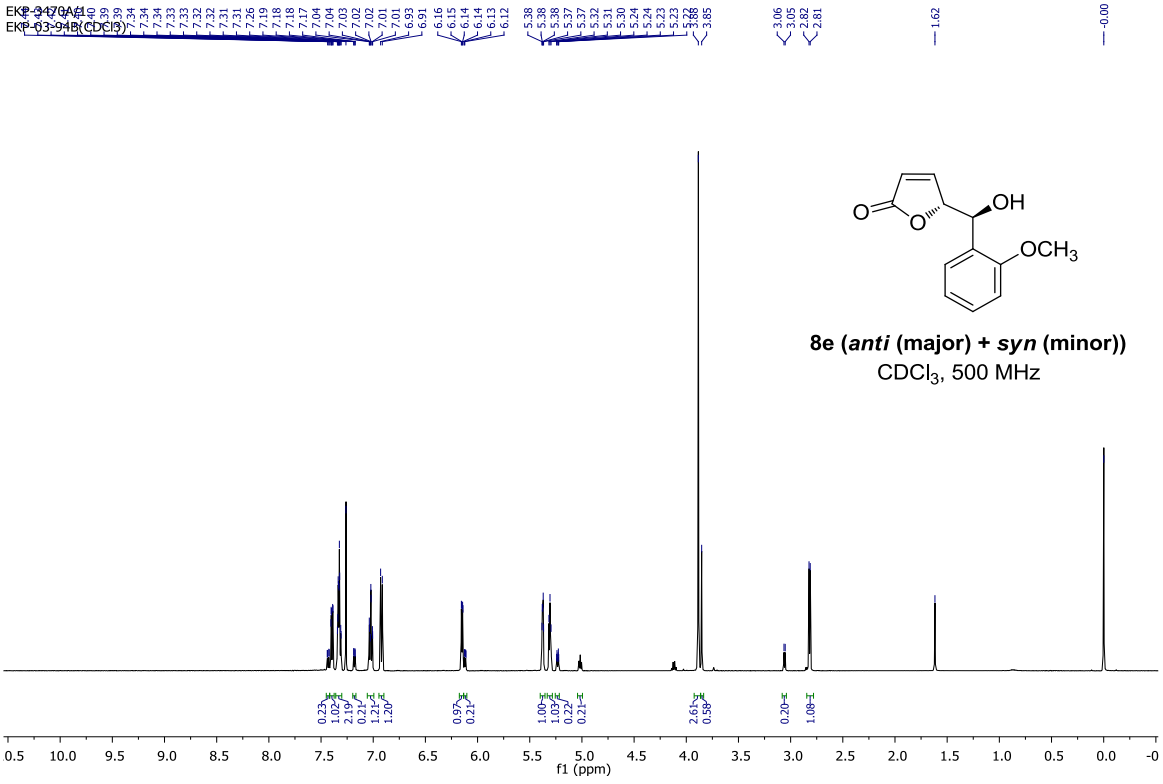
CH3
8b (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

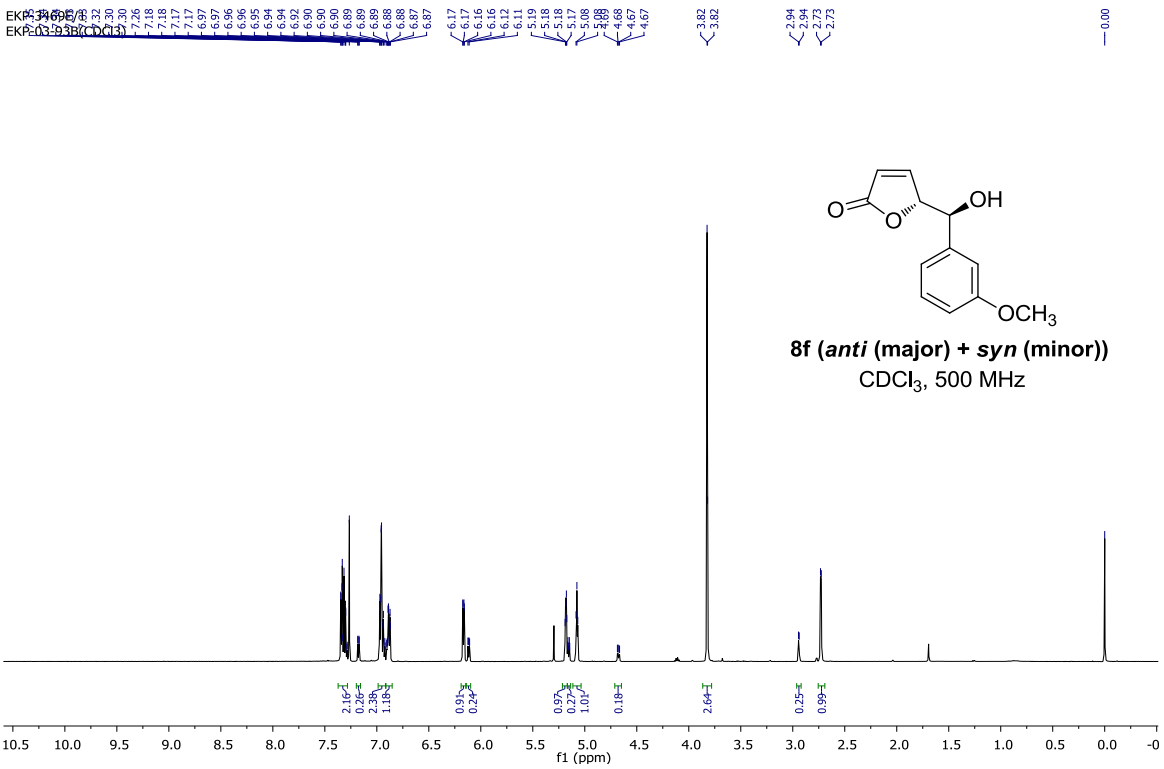

EKP-3465A/1
EKP-03-73B(CDCl3)
OH
Br
8c (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

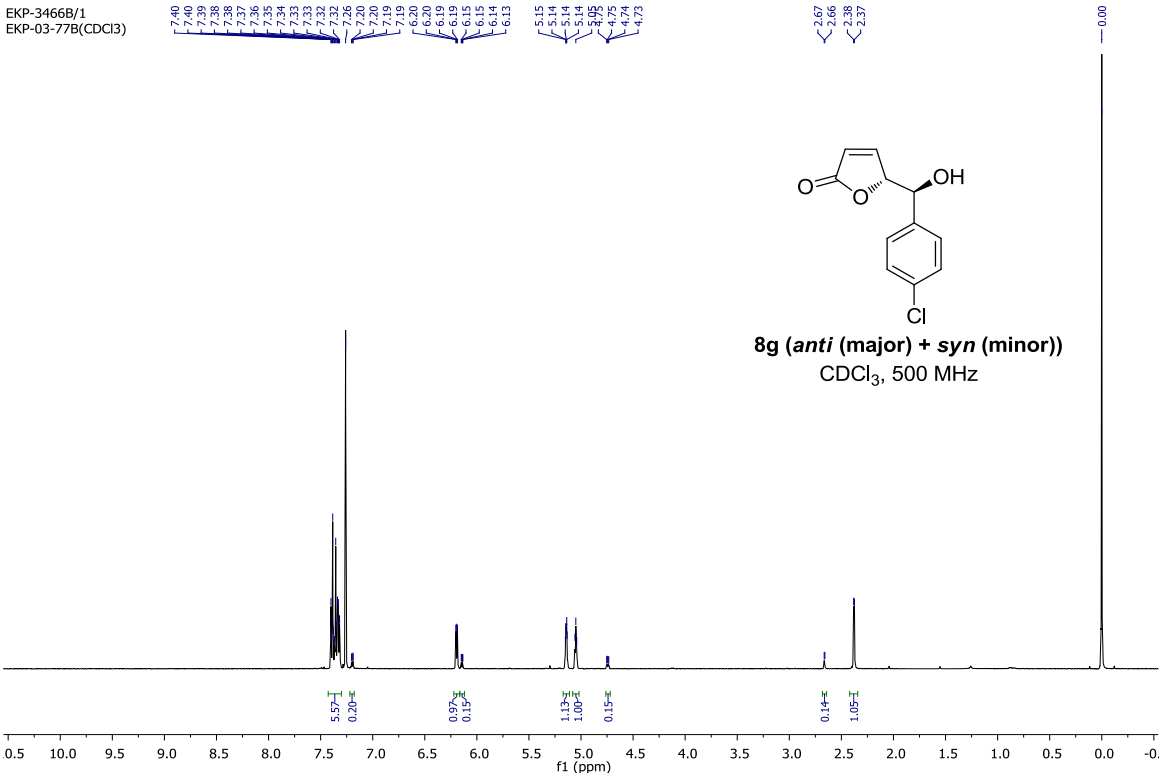


8d (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz

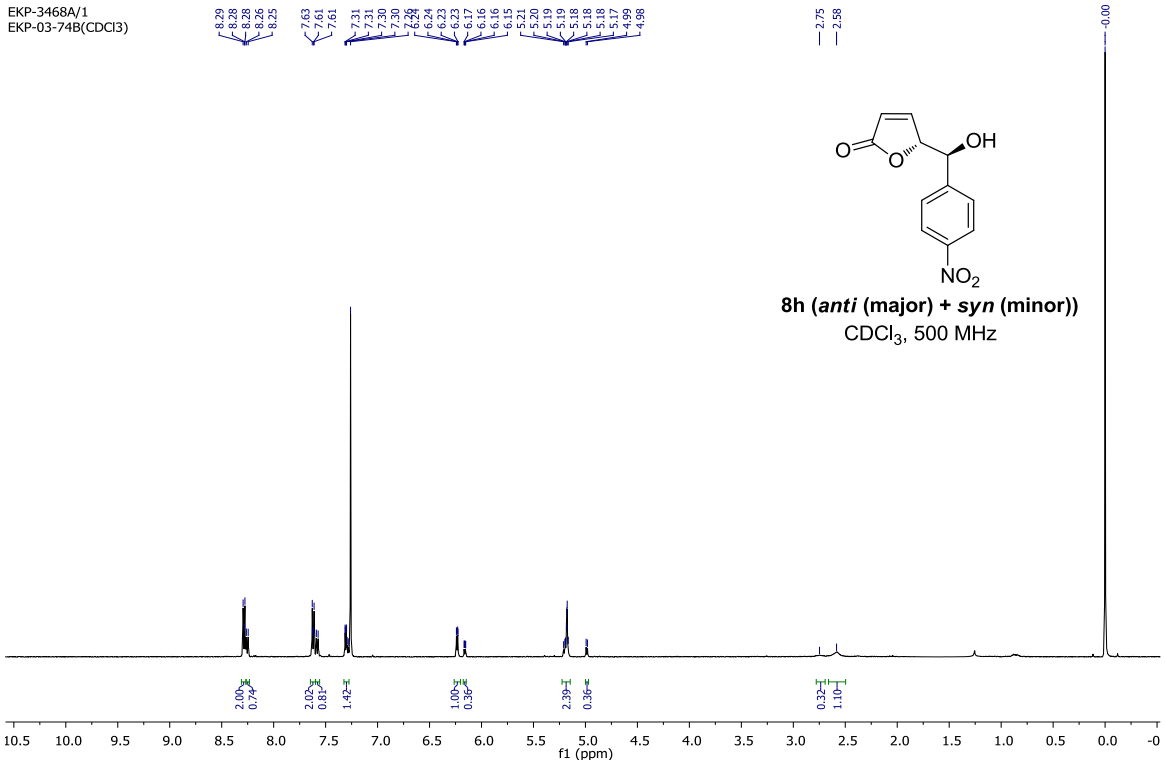


8e (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz


OH
O
O
OCH3
8f (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)


EKP-3466B/1
EKP-03-77B(CDCl3)
OH
O
O
Cl
8g (anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)

EKP-3468A/1
EKP-03-74B(CDCl3)



8h (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz

EKP-3465C/1
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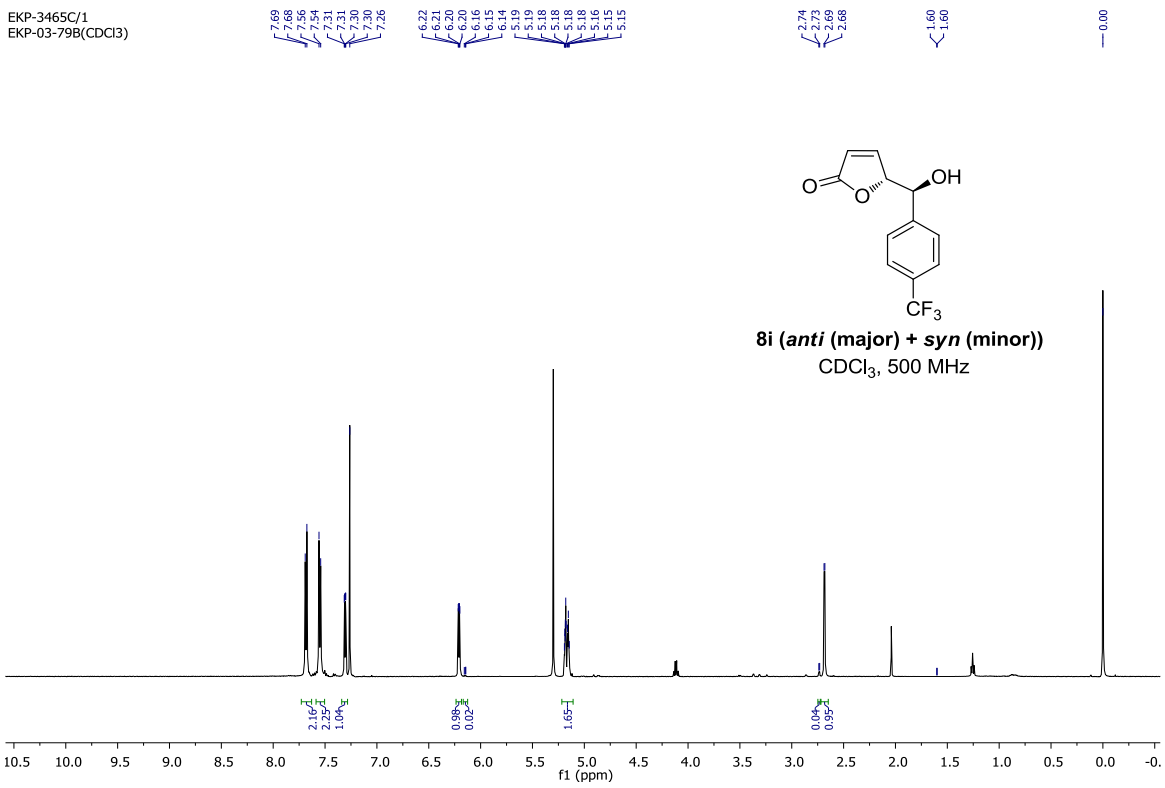
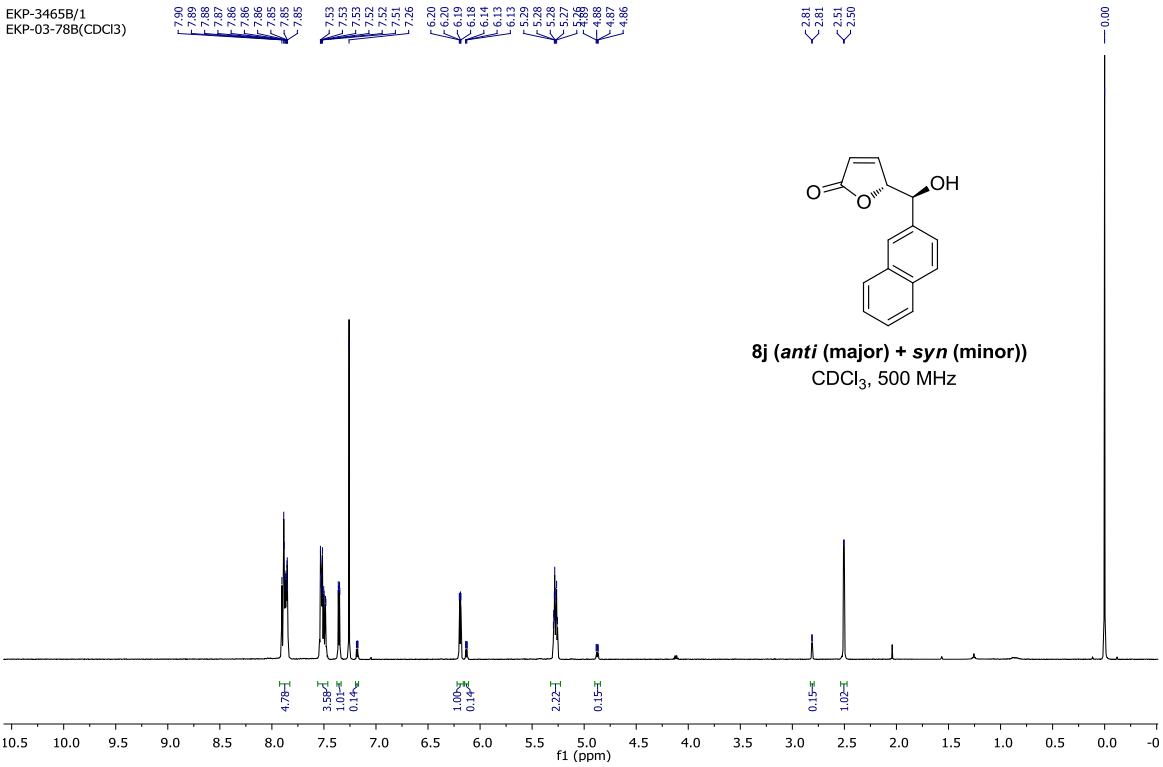


8i (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz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OH
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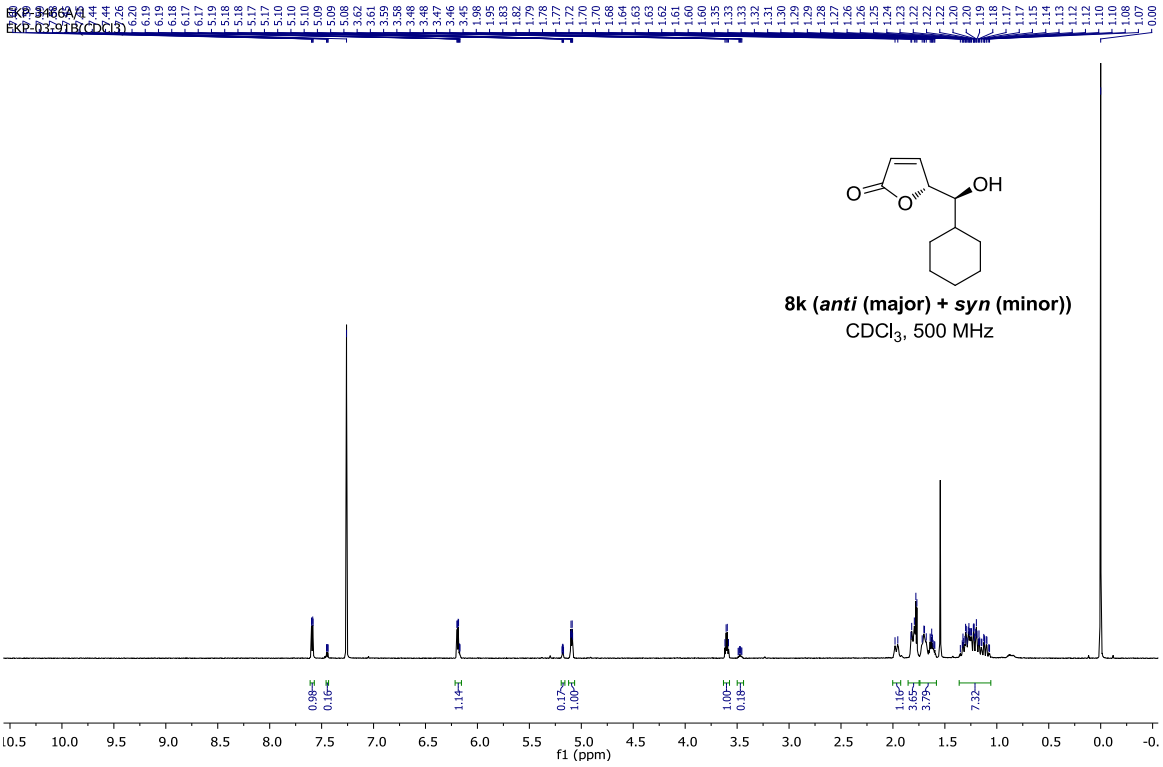
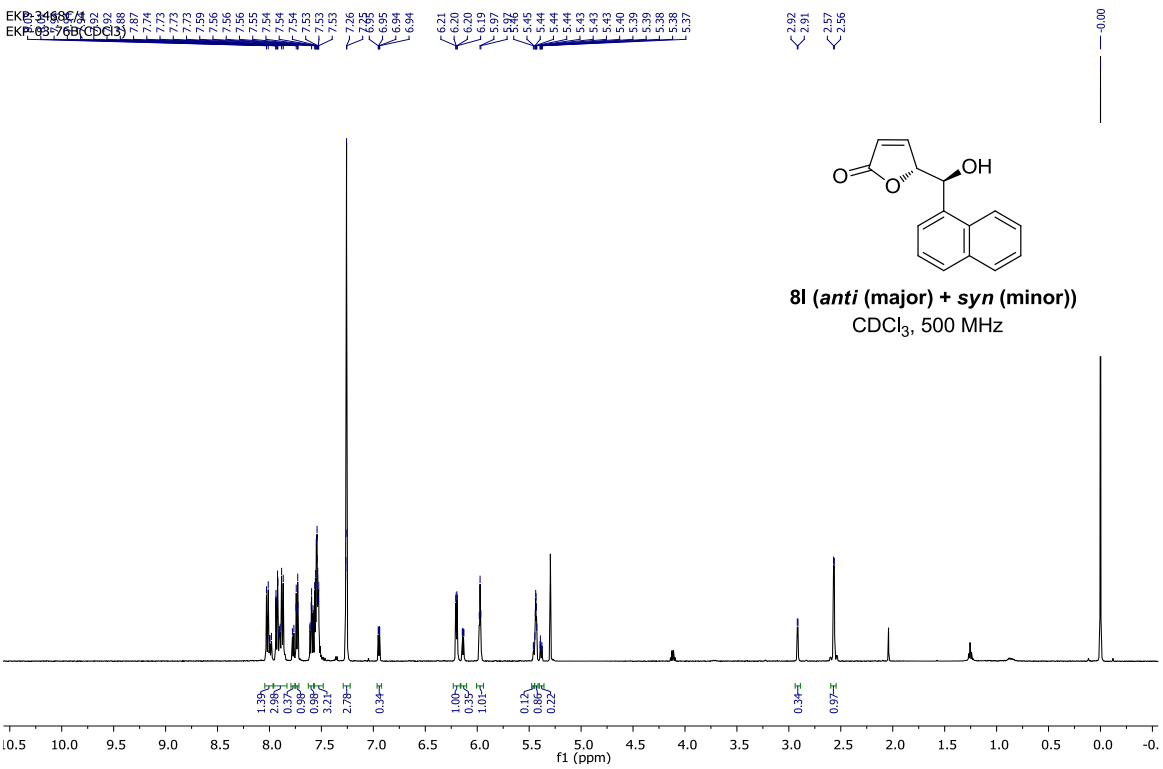
$CDCl_3$, 500 MHz
f1 (ppm)


OH
8k (*anti* (major) + *syn* (minor))
$CDCl_3$, 500 MHz
f1 (ppm)



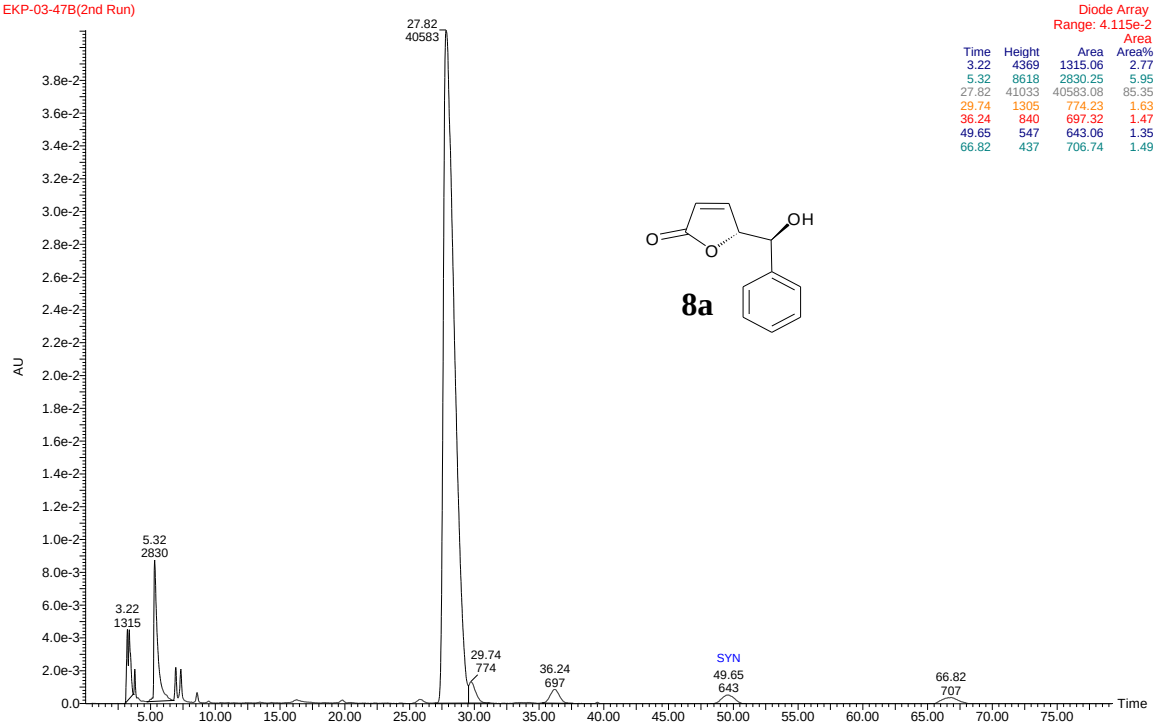
8l (*anti* (major) + *syn* (minor))

$CDCl_3$, 500 MHz

2.7 Selected HPLC chromatograms

AS-H 90hex 10ipa 254nm 90 min

EKP-03-47B(2nd Run)



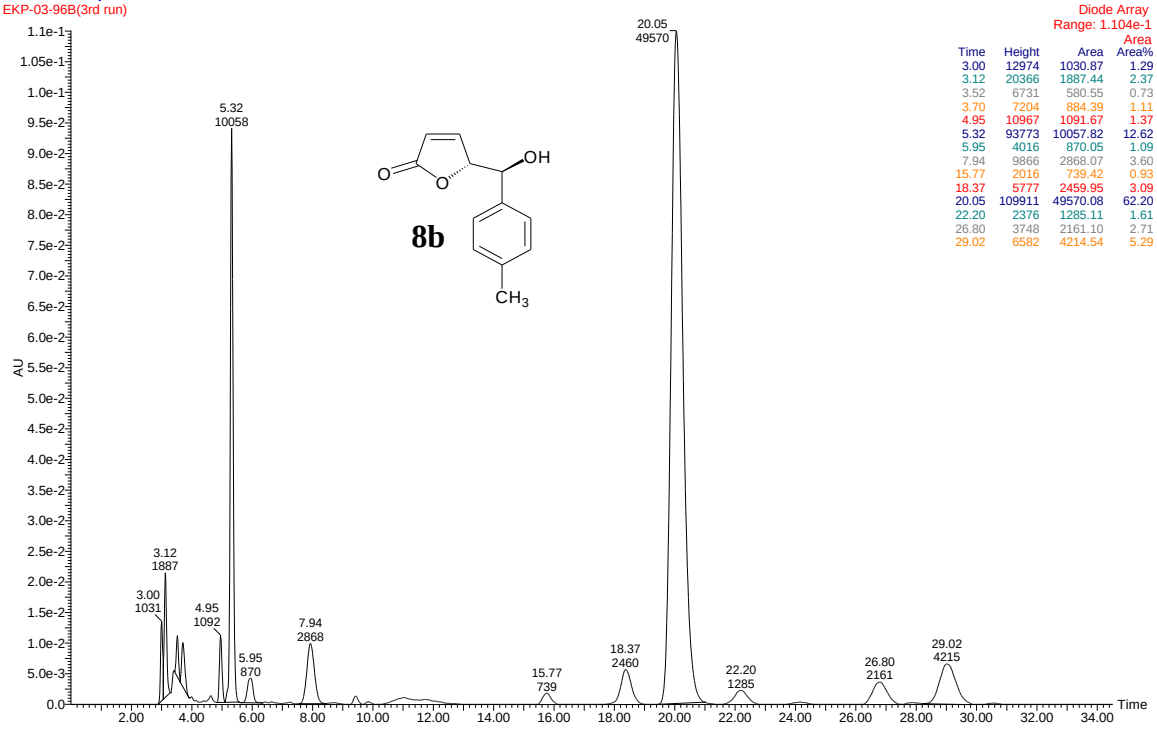
Diode Array
Range: 4.115e-2

Time	Height	Area	Area%
3.22	4369	1315.06	2.77
5.32	8618	2830.25	5.95
27.82	41033	40583.08	85.35
29.74	1305	774.23	1.63
36.24	840	697.32	1.47
49.65	547	643.06	1.35
66.82	437	706.74	1.49

8a

AD-H 95hex5ipa 254nm 60 min

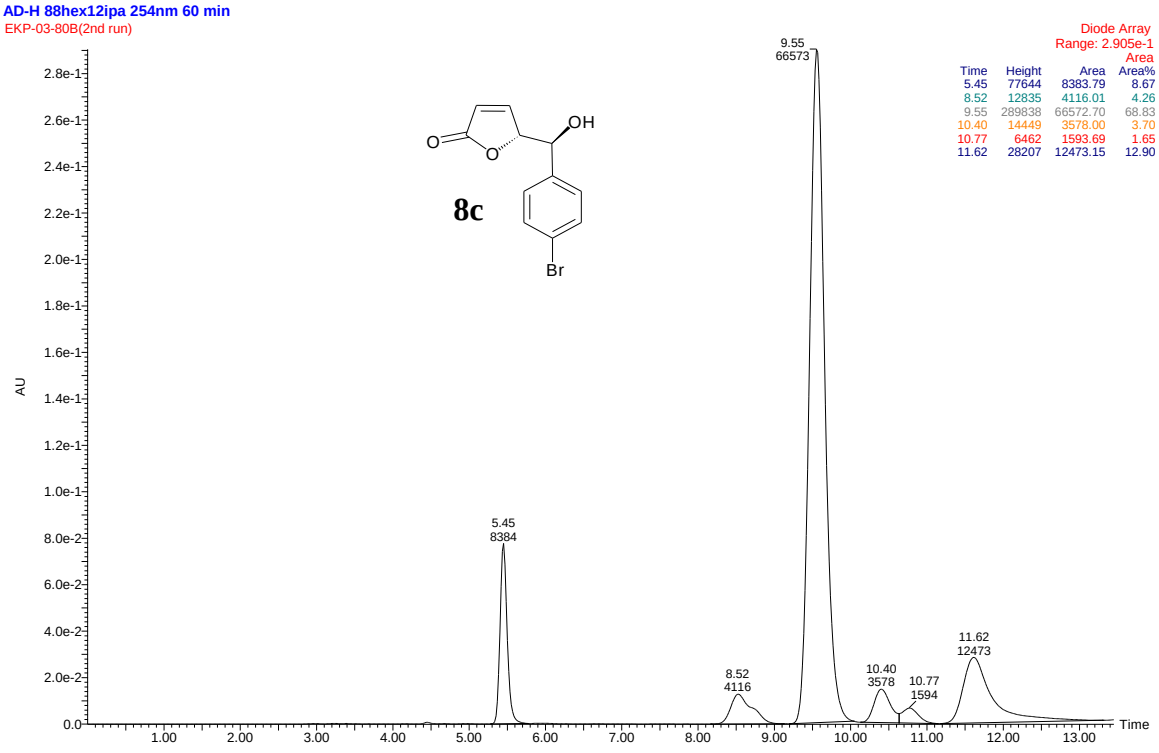
EKP-03-96B(3rd run)

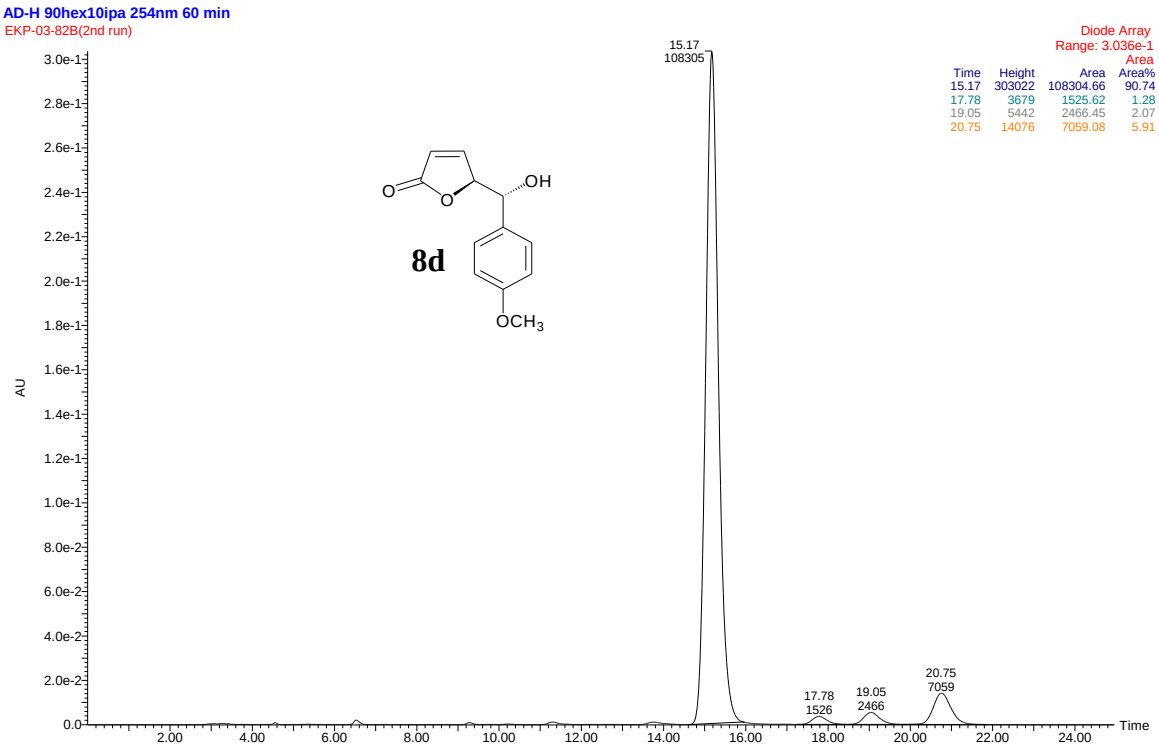


Diode Array
Range: 1.104e-1

Time	Height	Area	Area%
3.00	12974	1030.87	1.29
3.12	20366	1887.44	2.37
3.52	6731	580.55	0.73
3.70	7204	884.39	1.11
4.95	10967	1091.67	1.37
5.32	93773	10057.82	12.62
5.95	4016	870.05	1.09
7.94	9866	2868.07	3.60
15.77	2016	739.42	0.93
18.37	5777	2459.95	3.09
20.05	109911	49570.08	62.20
22.20	2376	1285.11	1.61
26.80	3748	2161.10	2.71
29.02	6582	4214.54	5.29

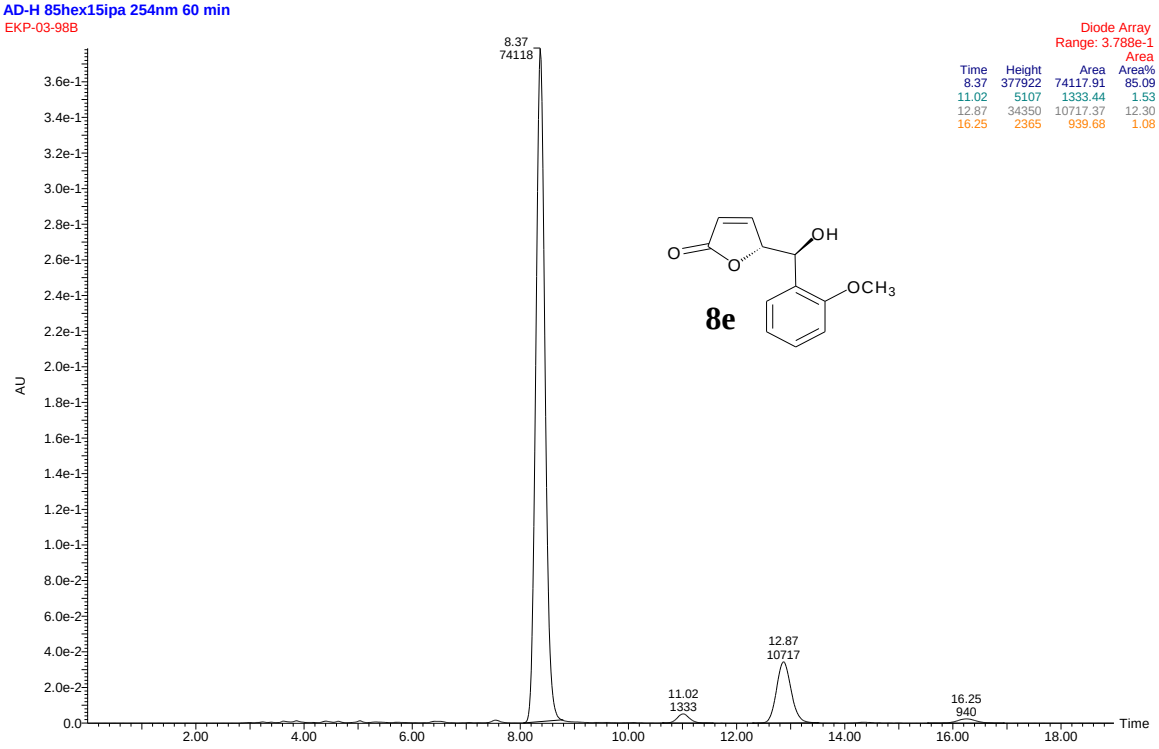
8b


AD-H 88hex12ipa 254nm 60 min
EKP-03-80B(2nd run)
Diode Array
Range: 2.905e-1
Area
Time Height Area Area%
5.45 77644 8383.79 8.67
8.52 12835 4116.01 4.26
9.55 289838 66572.70 68.83
10.40 14449 3578.00 3.70
10.77 6462 1593.69 1.65
11.62 28207 12473.15 12.90
8c
OH
O
O
Br
AU
Time
5.45
8384
8.52
4116
9.55
66573
10.40
3578
10.77
1594
11.62
12473


AD-H 90hex10ipa 254nm 60 min
EKP-03-82B(2nd run)
Diode Array
Range: 3.036e-1
Area
Time Height Area Area%
15.17 303022 108304.66 90.74
17.78 3679 1525.62 1.28
19.05 5442 2466.45 2.07
20.75 14076 7059.08 5.91
8d
OH
O
O
OCH3
AU
Time
15.17
108305
17.78
1526
19.05
2466
20.75
7059

AD-H 85hex15ipa 254nm 60 min

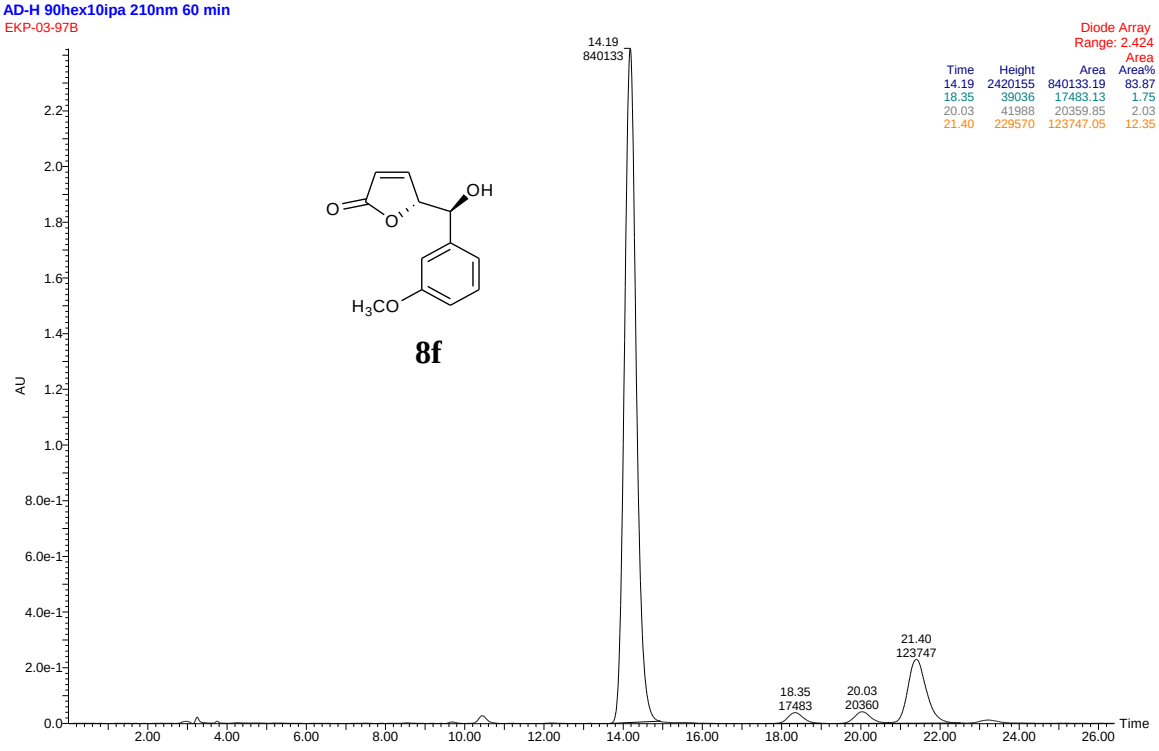
EKP-03-98B



8e

AD-H 90hex10ipa 210nm 60 min

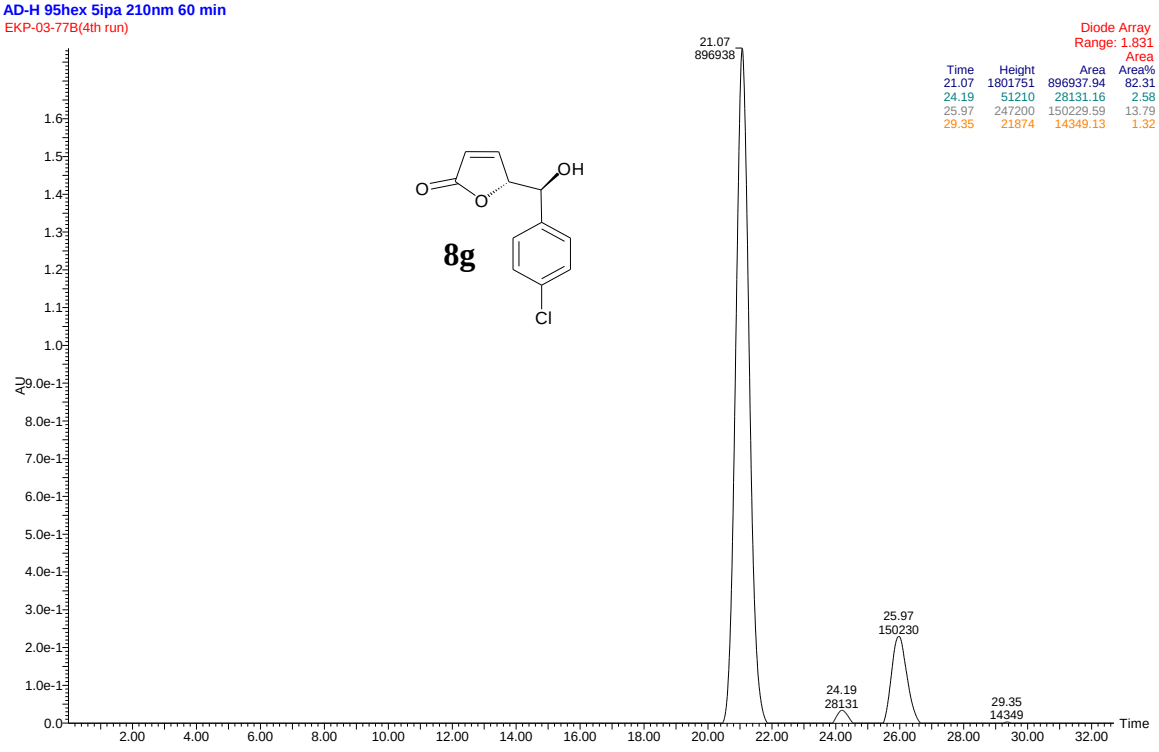
EKP-03-97B



8f

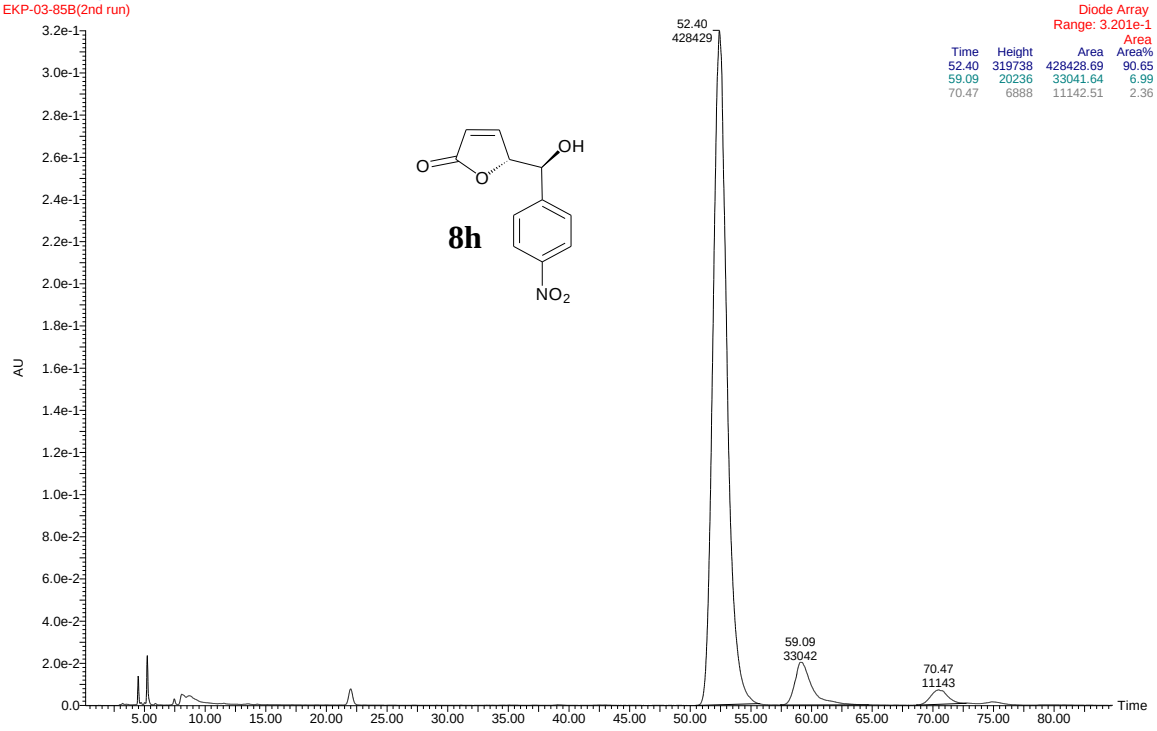
AD-H 95hex 5ipa 210nm 60 min

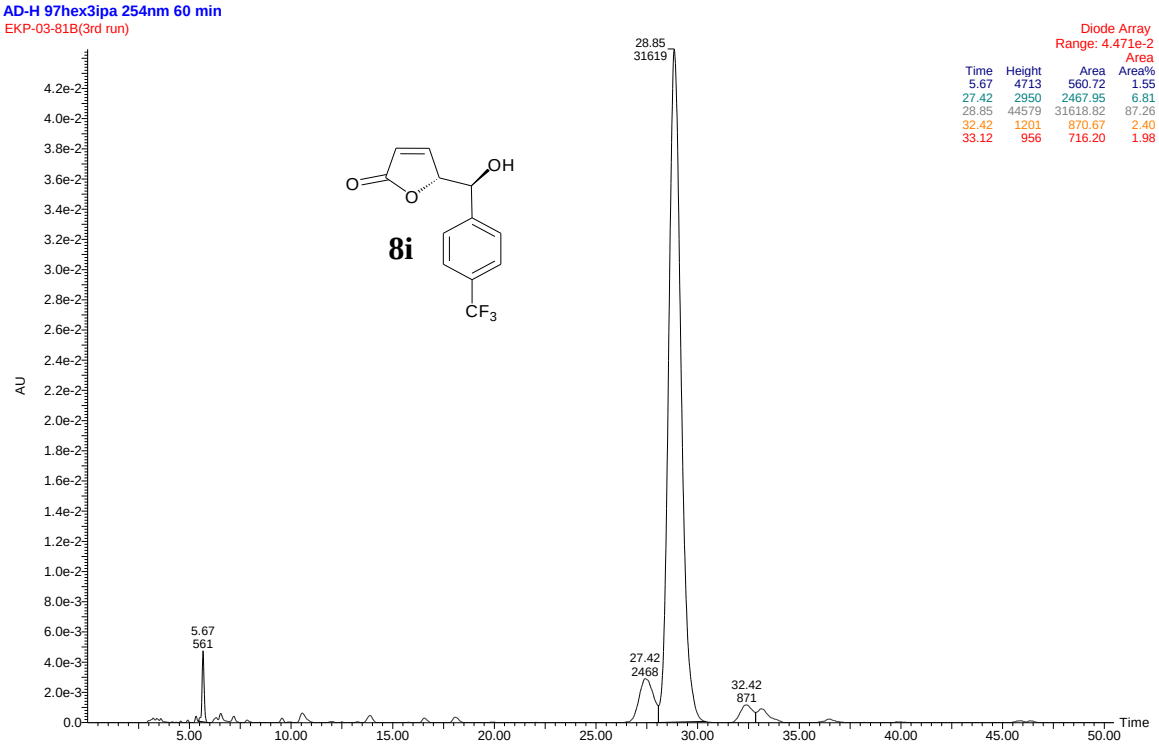
EKP-03-77B(4th run)

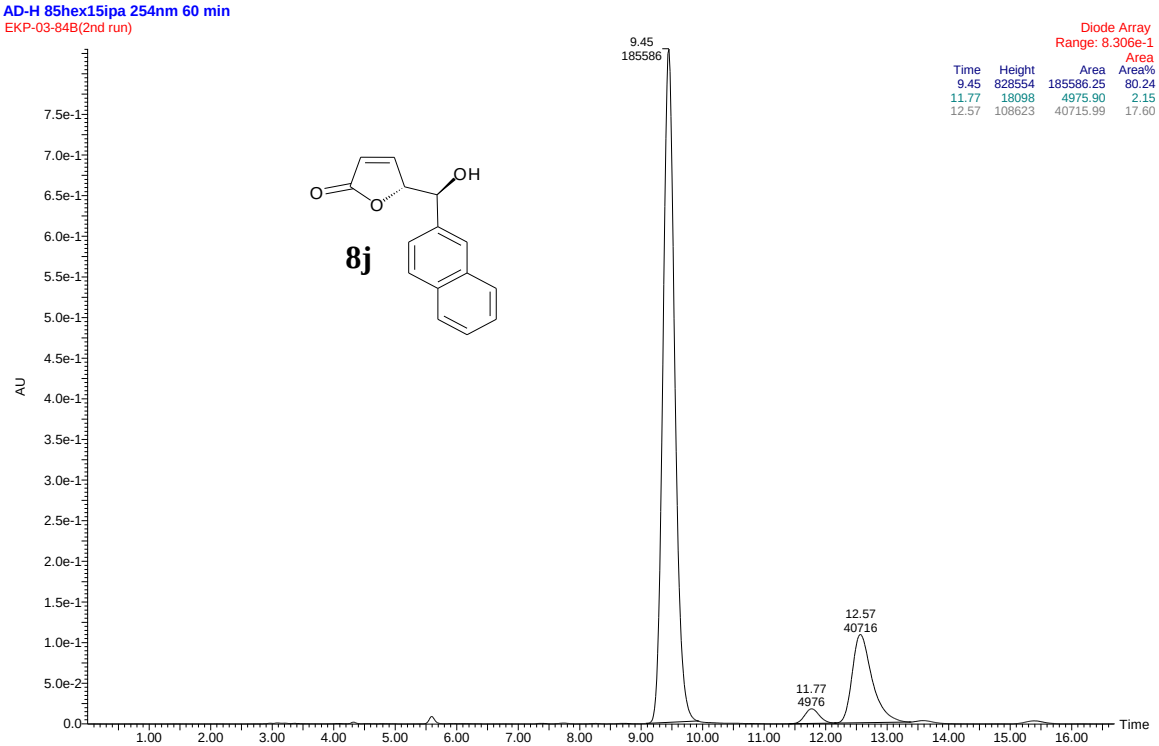


AD-H 95hex5ipa 254nm 120 min

EKP-03-85B(2nd run)

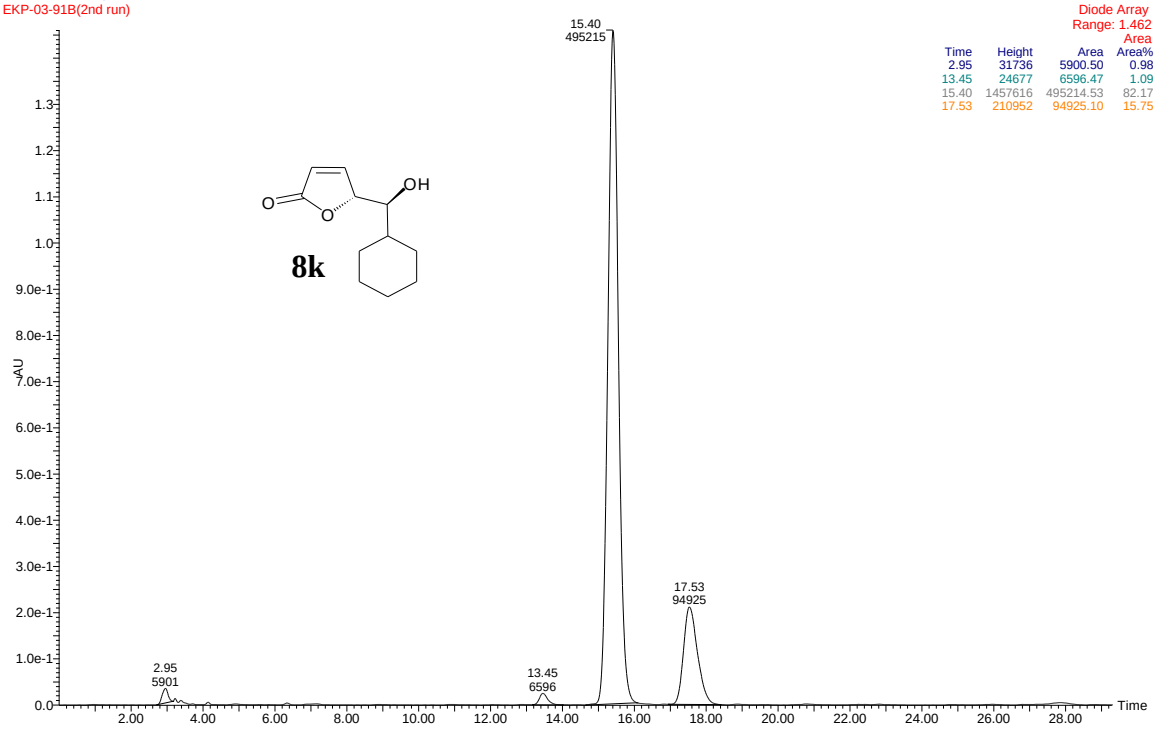



AD-H 97hex3ipa 254nm 60 min
EKP-03-81B(3rd run)
Diode Array
Range: 4.471e-2
Area
Time Height Area Area%
5.67 4713 560.72 1.55
27.42 2950 2467.95 6.81
28.85 44579 31618.82 87.26
32.42 1201 870.67 2.40
33.12 956 716.20 1.98
28.85
31619
OH
O
O
8i
CF3
5.67
561
27.42
2468
32.42
871
AU
Time


AD-H 85hex15ipa 254nm 60 min
EKP-03-84B(2nd run)
Diode Array
Range: 8.306e-1
Area
Time Height Area Area%
9.45 828554 185586.25 80.24
11.77 18098 4975.90 2.15
12.57 108623 40715.99 17.60
9.45
185586
OH
O
O
8j
12.57
40716
11.77
4976
AU
Time

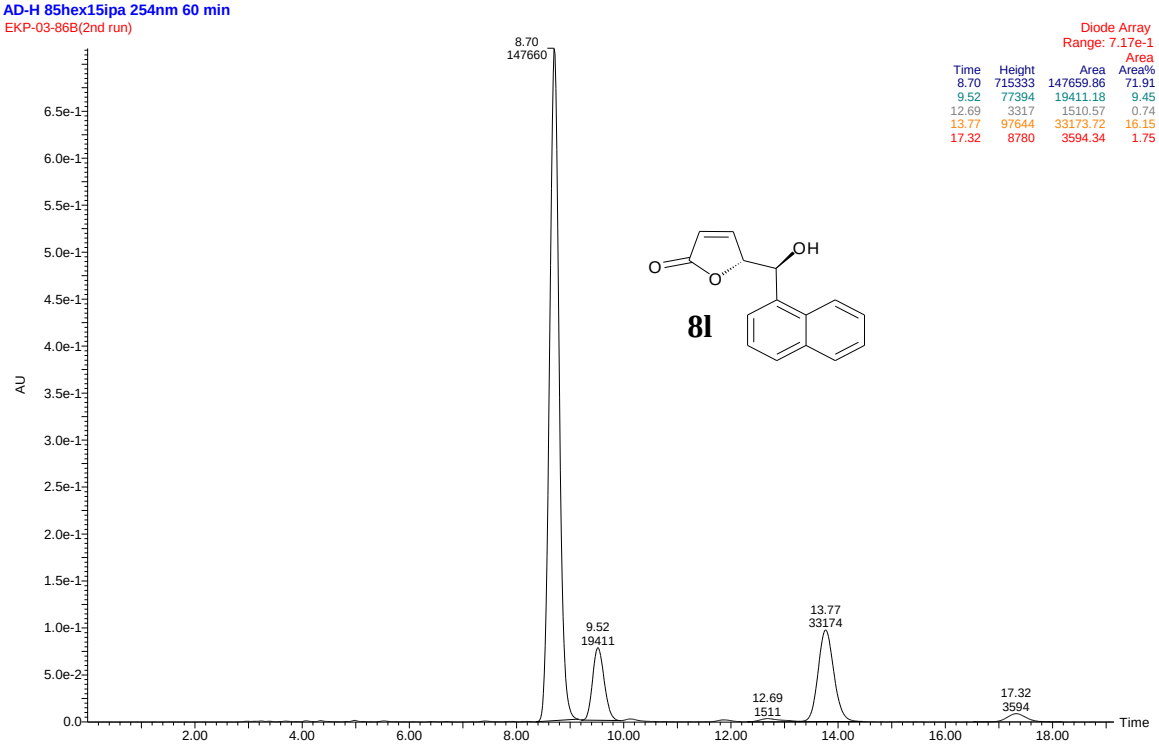
AD-H 95hex 5ipa 210nm 60 min

EKP-03-91B(2nd run)



AD-H 85hex15ipa 254nm 60 min

EKP-03-86B(2nd run)



CHAPTER 3

Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-Hydroxypipecolic Acid: Application of an Organocatalytic Direct Vinylogous Aldol Reaction

This Chapter is based on the following publication:

Pansare, S. V.; Paul, E. K. *Org. Biomol. Chem.* **2012,** *10,* 2119-2125.

Contributions of authors

S. V. Pansare: research supervisor, manuscript preparation.

E. K. Paul: experimental work, manuscript preparation.

3.1 Introduction

The piperidine motif is found in numerous biologically relevant natural products[1] as well as in medicinal and pharmaceutical agents,[2] and the synthesis of functionalized piperidines has therefore continued to engage synthetic chemists over the years.[3] Stereoselective routes to aryl substituted[4] and hydroxylated piperidines[5] have been extensively investigated. In particular, the biological activity and the synthesis of a variety of 2,3-disubstituted piperdines has attracted considerable interest. This is perhaps best exemplified by the synthetic efforts directed towards the neurokinin receptor antagonists (+)-L-733,060[6] and (+)-CP-99,994;[7] as well as (2*S*,3*R*)-3-hydroxypipecolic acid,[8] a constituent of the antibiotic tetrazomine (Figure 3.1). The following sections describe organocatalysis based enantioselective syntheses of these three targets.

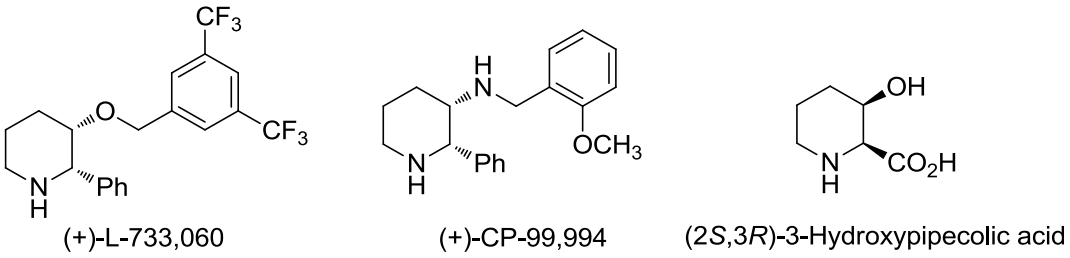


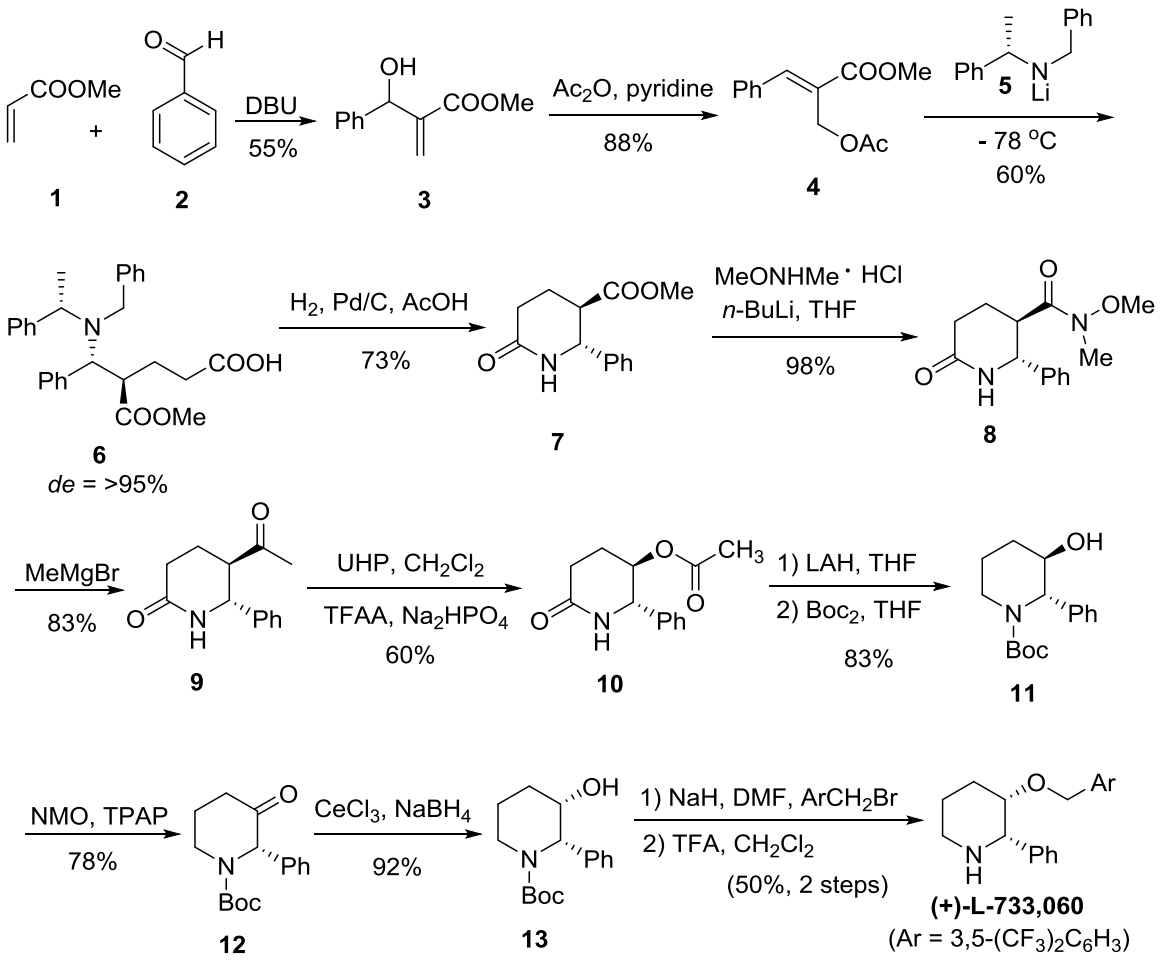
Figure 3.1. Biologically active 2,3-disubstituted piperidines targeted in this study.

3.2 Known synthetic routes to (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid

The following summary provides an overview of the reported syntheses of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid from 2010 onwards.

3.2.1 Synthesis of (+)-L-733,060

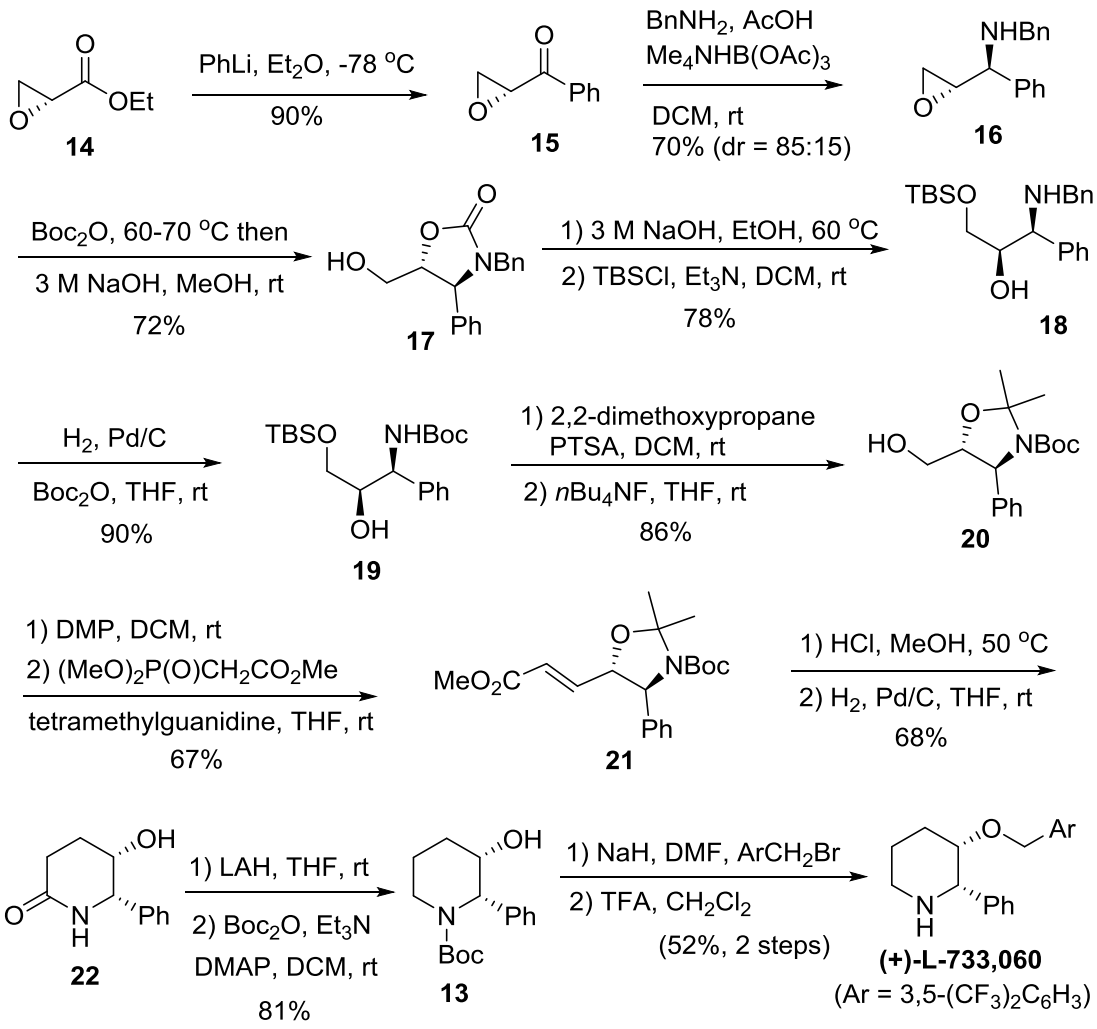
In 2010, Garrido and coworkers reported[6a] an enantioselective synthesis of (+)-L-733,060. The synthesis starts with the Baylis-Hillman reaction of methylacrylate **1** and benzaldehyde **2** (Scheme 3.1). The Baylis-Hillman adduct **3** obtained was treated with acetic anhydride and pyridine to give **4**. A domino reaction (stereoselective Ireland-Claisen rearrangement of the enolate derived from **4** followed by a Michael addition of **5** to the resulting compound) of **4** and chiral lithium amide **5** afforded optically pure γ-substituted δ-aminoacid **6**. Hydrogenolysis of **6** using Pd/C in AcOH and subsequent *in situ* lactamization gave **7**. The methyl ketone **9** was obtained by converting the piperidin-2-one **7** into Weinreb amide **8** followed by addition of methylmagnesium bromide. Baeyer-Villiger oxidation of **9** with urea hydrogen peroxide (UHP) provided lactam **10**. The lactam **10** was reduced using $LiAlH_4$ and subsequent treatment with $(Boc)_2O$, afforded the *N*-Boc amino alcohol **11**. The inversion of hydroxyl group is necessary for the synthesis of (+)-L-733,060. Oxidation of **11** with NMO/TPAP followed by stereoselective reduction using $CeCl_3$ and $NaBH_4$, gave the desired piperidine **13**. *O*-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzyl bromide followed by deprotection provided (+)-L-733,060 (12 steps from Baylis-Hillman adduct **3**, 5.6% overall yield).



Scheme 3.1. Synthesis of (+)-L-733,060 by Garrido.

In the same year, Haddad and coworkers reported[6b] the synthesis of (+)-L-733,060 (Scheme 3.2). The synthesis began with the addition of phenyllithium to ethyl glycidate **14** to provide epoxyketone **15**. Reductive amination of **15** gave the corresponding *anti* aminoepoxide **16** as a single diastereomer after flash chromatography. The aminoepoxide was treated with di-*tert*-butyldicarbonate to provide the oxazolidinone **17** through regioselective intramolecular epoxide opening. The oxazolidinone **17** was

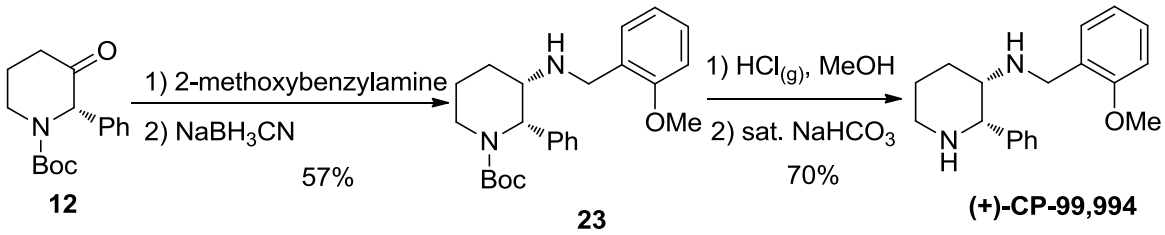
treated with NaOH/EtOH followed by a selective protection of the primary alcohol as *tert*-butyldimethylsilyl ether to provide the amino alcohol **18**. Hydrogenolysis of **18** with Pd/C in the presence of di-*tert*-butyldicarbonate afforded **19**. Oxazolidine **20** was obtained by the treatment of **19** with 2,2-dimethoxypropane followed by the deprotection of primary alcohol. Oxidation of **20** using Dess-Martin periodinane (DMP) gave the corresponding aldehyde, which was then subjected to a Horner-Wadsworth-Emmons reaction to provide the ester **21**. Unmasking of the 1,2-amino alcohol moiety in **21** followed by hydrogenation provided the saturated ester, which underwent *in situ* cyclization to form the piperidinone **22**. Reduction of **22** using $LiAlH_4$ followed by treatment with $(Boc)_2O$, provided the *N*-Boc aminoalcohol **13**. *O*-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzyl bromide followed by deprotection provided (+)-L-733,060 (16 steps from ethyl glycidate **14**, 5.3% overall yield).



Scheme 3.2. Synthesis of (+)-L-733,060 by Haddad.

3.2.2 Synthesis of (+)-CP-99,994

Garrido and coworkers reported[6a] an enantioselective synthesis of (+)-CP-99,994 (Scheme 3.3). The ketone **12** undergoes reductive amination followed by deprotection provided (+)-CP-99,994. The synthesis of ketone **12** is described in Scheme 3.1.



Scheme 3.3. Synthesis of (+)-CP-99,994 by Garrido.

In 2012, Bhat and coworkers reported[7d] an enantioselective synthesis of (+)-CP-99,994 (Scheme 3.4). The synthesis began with enantiomerically pure L-ornithine **24**, which was protected with benzyl chloroformate to afford **25** in excellent yield. Compound **25** was converted to *N*-methoxy-*N*-methylamide **26** which was treated with phenylmagnesium bromide at -78 ^{o}C in THF to provide ketone **27**. The diaminophenylketone **27** was treated with trimethylsilyl triflate and triethylsilane at -78 ^{o}C to afford the piperidine derivative **28** with good diastereoselectivity (24/1) resulting from cyclization of **27** *via* an *N*-acyliminium ion. Deprotection of **28** followed by reductive *N*-alkylation of the primary amine with 2-methoxybenzaldehyde provided CP-99,994 (7 steps from L-ornithine **24**, 40% overall yield).

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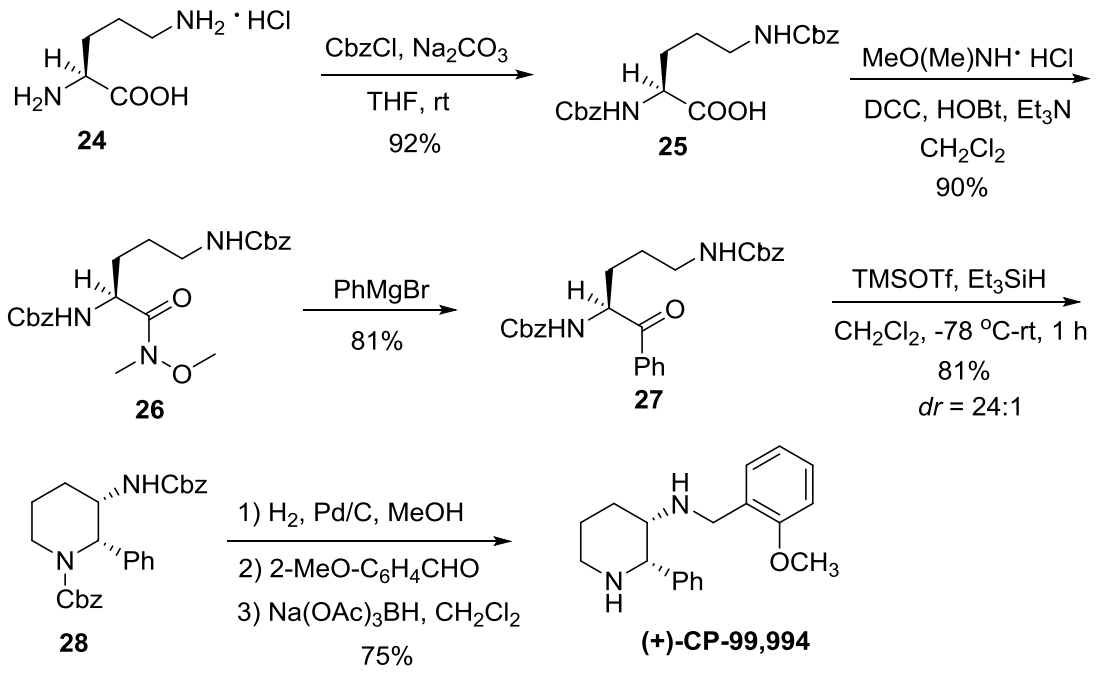
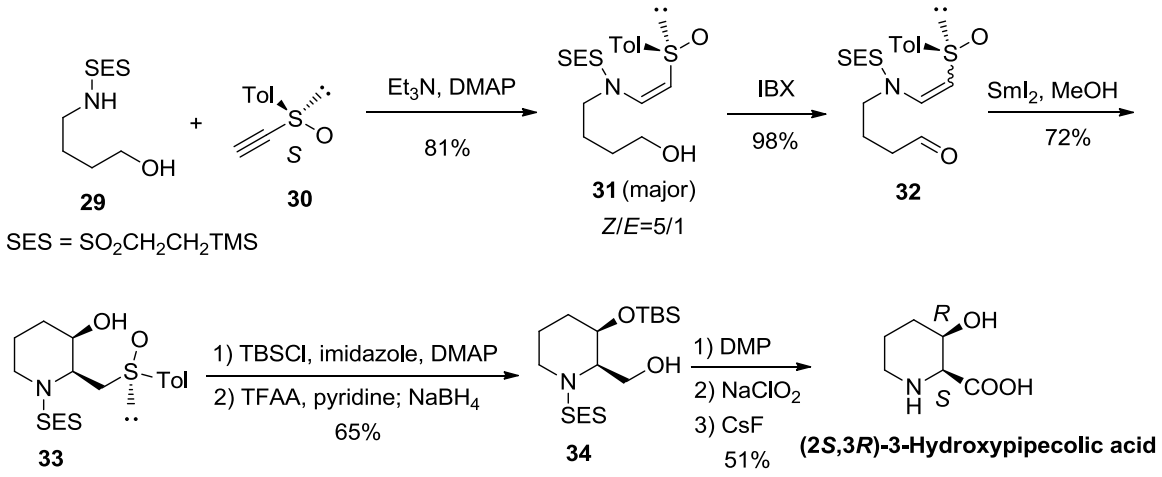


Scheme 3.4. Synthesis of (+)-CP-99,994 by Bhat.

3.2.3. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid

In 2010, Lee and coworkers reported[8b] a synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid. The synthesis started from monoprotected amino alcohol **29** (Scheme 3.5), which was obtained from butane-1,4-diol in three steps. The amino alcohol **29** was added to optically active acetylenic sulfoxide **30** under basic conditions (Et_3N, DMAP) to afford sulfonamide **31** as a 5/1 *Z*:*E* mixture. After separation, *Z*-**31** was oxidized to aldehyde **32** with 2-iodoxybenzoic acid (IBX). A highly diastereoselective radical cyclization took place, when aldehyde **32** was treated with SmI_2 in methanol and the only product formed was the 3-hydroxypiperidine **33** (*dr* = 100:0, 72%). After protection of the alcohol as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole, DMAP), a Pummerer rearrangement

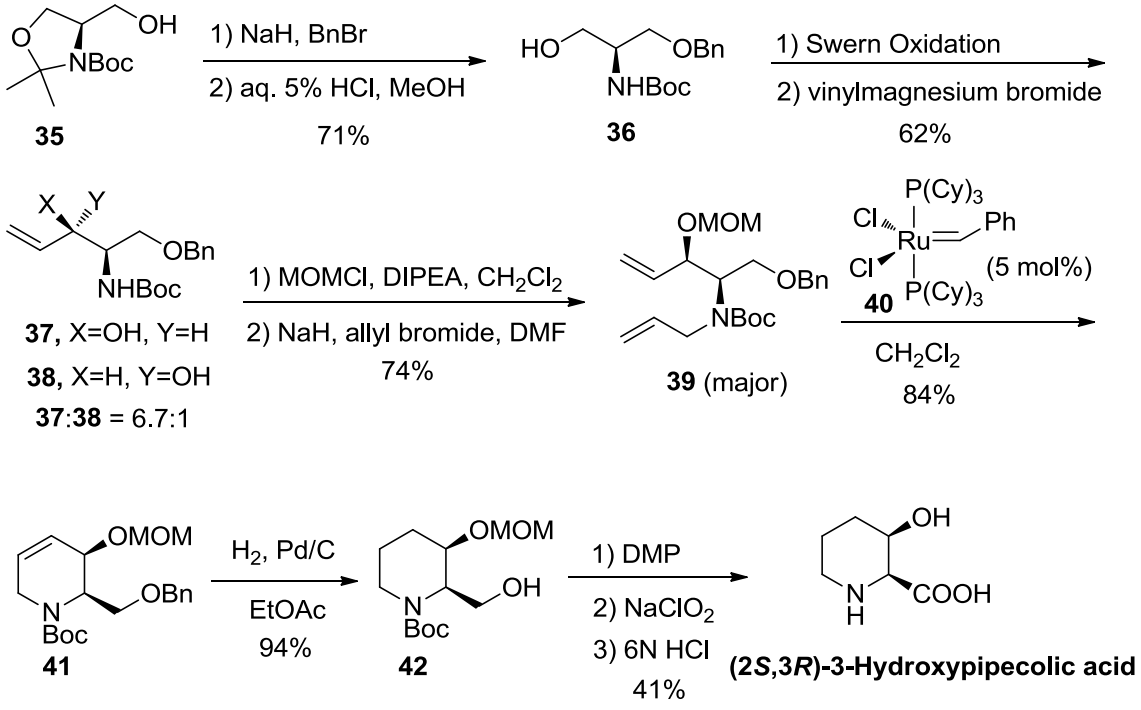
was performed and reduction of the Pummerer product gave the primary alcohol **34**. The hydroxypiperidine **34** was oxidized in two steps (DMP, followed by $NaClO_2$) to the corresponding carboxylic acid. After a deprotection with cesium fluoride, (2*S*,3*R*)-3-hydroxypipecolic acid was obtained (8 steps from **29**, 19% overall yield).



Scheme 3.5. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid by Lee.

A strategy involving ring-closing metathesis (RCM) to build the piperidine core of 3-hydroxypipecolic acid by C–C bond formation was reported recently by Chattopadhyay.[8f] Serinol derivative **35** was protected as a benzyl ether followed by the oxazolidine ring opening under acidic conditions to provide **36** (Scheme 3.6). Swern oxidation of **36** provided the corresponding aldehyde. Treatment of the aldehyde with vinylmagnesium bromide afforded *syn*-allylic alcohol **37** as the major isomer (*dr* = 6.7:1). Unfortunately, the *syn* isomer could not be separated from the minor *anti* isomer **38**. After conversion of the mixture of **37** and **38** into their MOM ether derivatives and *N*-

allylation (NaH, allyl bromide), the pure *syn* isomer **39** was separated by column chromatography. Ring-closing metathesis (RCM) of **39** with the first-generation Grubbs catalyst **40** gave the desired dehydropiperidine derivative **41**. Hydrogenation of **41** afforded the piperidine derivative **42**, which was subjected to a two-step oxidation (DMP and Pinnick oxidation) to furnish the carboxylic acid. Deprotection of the Boc and MOM groups under acidic conditions provided the desired (2*S*,3*R*)-3-hydroxypipecolic acid (11 steps from **35**, 10.5% overall yield).



Scheme 3.6. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid by Chattopadhyay.

3.3 Results and Discussions

The 2-substituted 3-hydroxy piperidine motif **A** is accessible by the rearrangement of 5-(1-aminoalkyl or -aminoaryl) butyrolactones **B** (Figure 3.2).[9] The aminobutyrolactones can, in turn, be obtained from the corresponding hydroxy precursors **C**, which are typically obtained by stereoselective vinylogous Mukaiyama aldol reactions of 2-siloxyfurans and aldehydes.[10] However, a much simpler route to stereodefined 5-(1-hydroxyalkyl/aryl) butenolides involves the organocatalytic, direct vinylogous aldol reaction of γ-crotonolactone (2(5*H*)-furanone) with aldehydes, a reaction that has received attention only recently.[11] Given the structural similarities in the targets of the present study (Figure 3.1), it appeared that a suitably functionalized butyrolactone could potentially be employed as a common synthetic precursor to achieve most of the objectives. In addition, this synthetic strategy would also highlight the utility of the organocatalytic direct vinylogous aldol (ODVA) reaction (Figure 3.2).

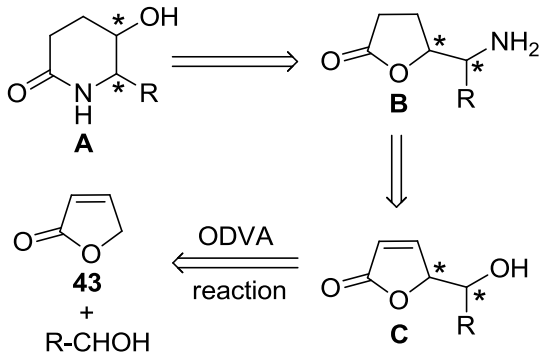
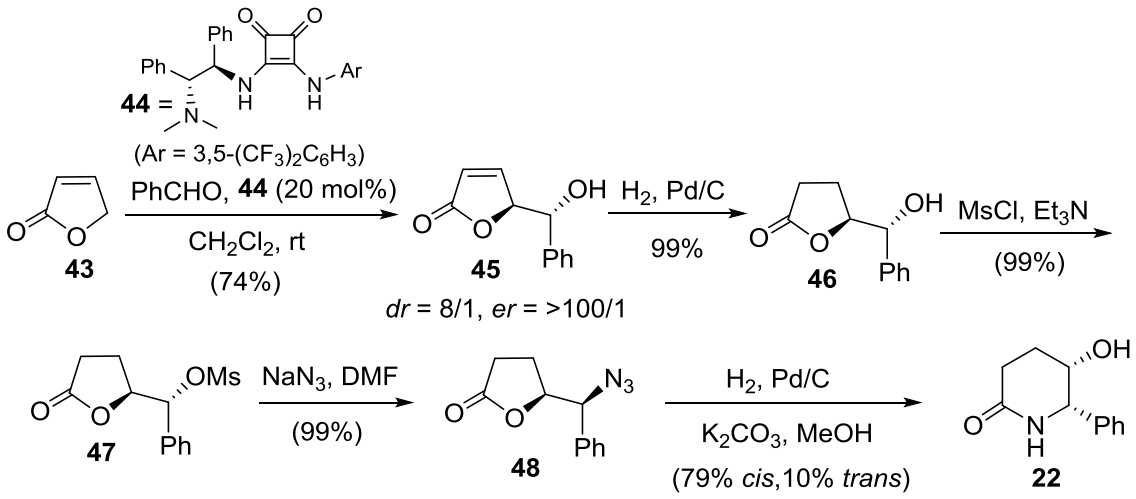


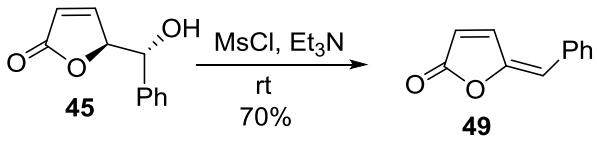
Figure 3.2. The organocatalytic direct vinylogous aldol route to functionalized piperidines.

Our studies therefore began with the synthesis of **45** (Scheme 3.7) and its conversion to (5*S*,6*S*)-5-hydroxy-6-phenylpiperidin-2-one (**22**) which is an advanced precursor to (+)-L-733,060 and (+)-CP-99,994. Initially, the direct vinylogous aldol reaction of commercially available *γ*-crotonolactone and benzaldehyde was examined in the presence of selected aminothiourea and aminosquaramide catalysts derived from diphenylethylenediamine, 1,2-cyclohexane diamine and amines obtained from cinchona alkaloids. The details of these studies were described in Chapter 2 (pages 27-32). Extensive optimization studies with these catalysts revealed the aminosquaramide **44**[12] as the most efficient catalyst in terms of the yield, diastereoselectivity and enantioselectivity for the aldol product.[11c] Thus, the direct vinylogous aldol reaction of *γ*-crotonolactone with benzaldehyde provided the butenolide **45** in good yield and diastereoselectivity (74%, *anti*/*syn* = 8/1) and excellent enantiomeric excess (>99% *ee* for the *anti* diastereomer) when the reaction was conducted in dichloromethane at ambient temperature (Scheme 3.7).



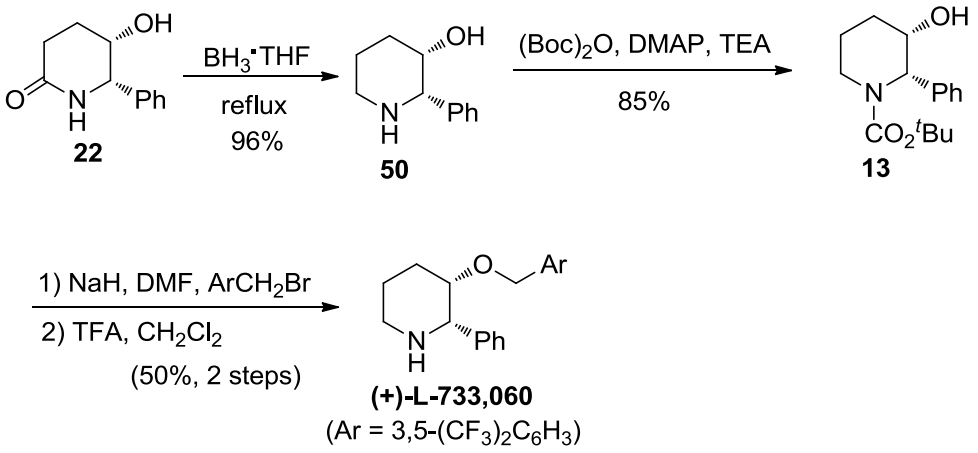
Scheme 3.7. Conversion of aldol product to lactam employing ODVA reaction.

The aldol product **45** (as a diastereomeric mixture) was easily converted to the lactam **22** *via* a series of simple transformations. Hydrogenation of **45** to the butyrolactone **46**, subsequent mesylation of the secondary alcohol to give **47** and displacement of the mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **48**. It should be mentioned that the attempted mesylation of **45** exclusively resulted in its dehydration (Scheme 3.8).



Scheme 3.8. Dehydration of aldol product.

The unwanted dehydration side reaction is effectively prevented by prior reduction of the double bond in **44**. Reduction of the azide (H_2, Pd/C) generated a mixture of the corresponding amino butyrolactone and the required piperidone **22** resulting from an intramolecular *N*-acylation of the amino lactone. Notably, hydrogenation of the azide in the presence of a base (K_2CO_3) significantly facilitated this rearrangement to directly provide **22** without any residual amino lactone. At this stage, *cis*-**22** was easily separated from the minor (*trans*) diastereomer by flash chromatography and all further transformations were carried out with diastereomerically pure *cis*-**22**. The overall conversion of **44** to **22** is quite efficient (76% yield over four steps) and can be conducted without purification of any of the intermediates.

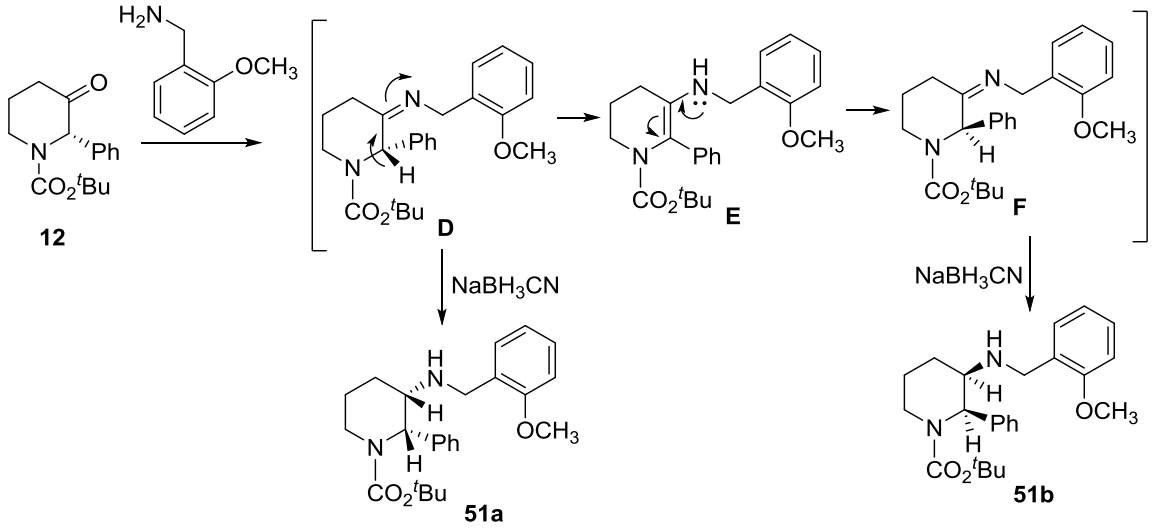


Scheme 3.9. Synthesis of (+)-L-733,060.

Reduction of the piperidinone **22** with borane[6e] provided the corresponding piperidine (**50**, 96%) (Scheme 3.9), which was converted to the *N*-Boc derivative **13**. The conversion of **13** to the neurokinin receptor antagonist targets was achieved by adaptation and some modification of previously described methods (Scheme 3.9). *O*-Alkylation of **13** with 3,5-bis(trifluoromethyl)benzylbromide followed by deprotection provided (+)-L-733,060 (9 steps from benzaldehyde, 24.8% overall yield).

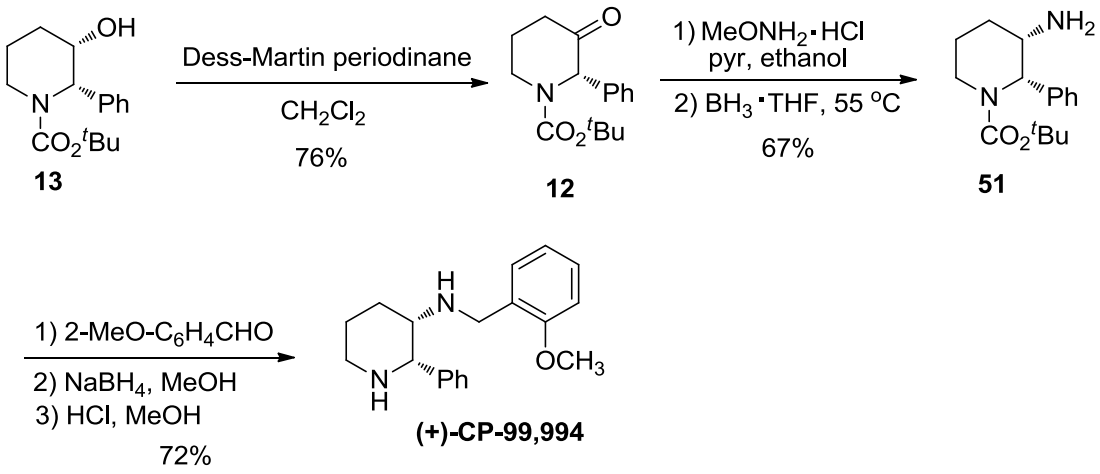
The synthesis of (+)-CP-99,994 required the synthesis of ketone **12** and subsequent reductive amination (Scheme 3.11), and both of these steps required detailed attention to the reaction conditions. Oxidation of **13** with Dess-Martin periodinane provided the 3-piperidinone **12** (77%, 94% *ee*). Notably, in our hands, the enantiomeric excess of **12** was dependent on the method of oxidation and the DMP procedure[13] is by far the best for obtaining **12** in good yield and high enantiomeric excess. Oxidation of **13** with IBX or IBX/DMSO with heating led to **12** with diminished *ee* as compared to **13**. Swern oxidation of **13** is reported to provide **12** without racemization.[14] In the present

study, Swern oxidation of **13** (96% *ee*) provided **12** with 76% *ee*. Oximation of **12** obtained *in situ* from the Swern oxidation of **13** (*ee* of **13** = 93%), eventually provided CP-99,994 with 60% *ee*. Similarly, the reaction of **12** (87% *ee*) with methoxylamine hydrochloride in pyridine as the solvent[13] subsequently provided CP-99,994 with 50% *ee*. Changing the solvent to ethanol and employing only the necessary amount of pyridine was found to be important for minimizing the racemization of **12**. Likewise, direct imination of **12** with the appropriate amine (see the reported conversion of **12** to **23** described in Scheme 3.3, page 73),[6a] with or without Lewis acid catalysis, eventually provided racemic CP-99,994. These observations suggest that **12** is prone to racemization if it is heated or exposed to excess base and that the extent of racemization, under these conditions, may depend on variables that are difficult to regulate. A proposed mechanism for the racemization of **12** is shown in Scheme 3.10.



Scheme 3.10. A proposed mechanism for the racemization of **12**.

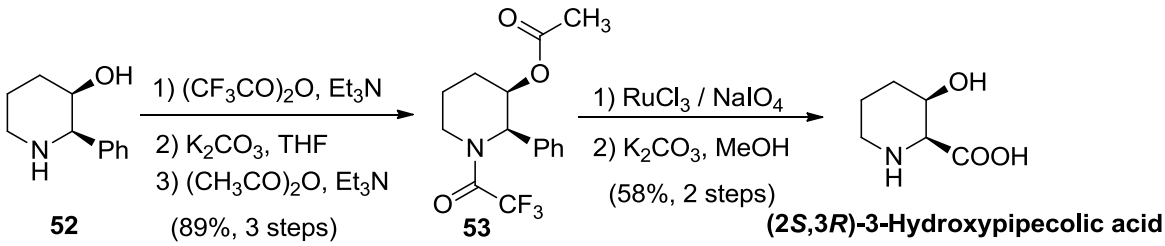
Oximation of **12** with methoxylamine by a significant modification of the reported procedure[13] (ethanol instead of pyridine as the solvent) gave the corresponding oxime ether which was reduced stereoselectively to the amine **51** (Scheme 3.11). Reductive *N*-alkylation of **51** with 2-methoxybenzaldehyde followed by deprotection provided (+)-CP-99,994 (11 steps from benzaldehyde, 16.9% overall yield).



Scheme 3.11. Synthesis of (+)-CP-99,994 employing ODVA reaction.

We next investigated the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid. This particular diastereomer of 3-hydroxypipecolic acid has been the subject of numerous investigations and it continues to attract interest from synthetic chemists.[8a-f] At the outset, it seemed reasonable that direct oxidation of the phenyl ring in the *O*-acetyl derivative of *N*-Boc-(2*R*,3*R*)-2-phenyl-3-hydroxypiperidine (*ent*-**13**), which was obtained by employing the enantiomer of catalyst **44**, would lead us to the pipecolic acid target.

However, attempted oxidation[15] ($RuCl_3/NaIO_4$) of this substrate invariably led to a mixture of products, none of which corresponded to the required carboxylic acid. Interestingly, a change in the *N*-protecting group[8c,16] was beneficial. Accordingly, (2*R*,3*R*)-2-phenyl-3-hydroxypiperidine **52** was first converted to the *N*,*O*-bis (trifluoroacetyl) derivative and the trifluoroacetate ester was selectively replaced with an acetate to provide **53** (Scheme 3.12). Oxidation of the phenyl ring in **53**, with $RuCl_3/NaIO_4$, now proceeded smoothly to provide the corresponding carboxylic acid. Methanolysis of the trifluoroacetamide and the acetate in this intermediate gave (2*S*,3*R*)-3-hydroxypipecolic acid (10 steps from benzaldehyde, 28.1% overall yield).



Scheme 3.12. Synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid from **52**.

3.4 Conclusions

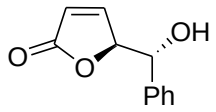
In conclusion, we have achieved the synthesis of three representative members of the 2,3-disubstituted class of bioactive piperidines from the butenolide **45**. The syntheses developed in this study are based on an organocatalytic vinylogous aldol reaction as the pivotal step. Notably, ketone **12** is also a starting material in the synthesis of spirocyclic NK-1 receptor antagonists.[14b,17] The methodology presented here has potential use in the

preparation of libraries of antagonists, related to the those described here, by variation of the aldehyde in the direct vinylogous aldol step.

3.5 Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. Compounds **45**, **13**, **13a** and **51a** were prepared by literature methods. The conversion of **13a** to (+)-L-733,060 and of **51a** to (+)-CP-99,994 was achieved by literature methods.

(*S*)-5-[(*R*)-Hydroxy(phenyl)methyl]furan-2(5*H*)-one (45):

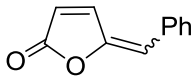


To the catalyst (20 mol %, 1.0 g) in a 25 mL round bottom flask was added benzaldehyde (970 µL, 9.14 mmol) followed by 2-(5*H*)-furanone **43** (1.28 mL, 18.3 mmol) and dichloromethane (5.0 mL). The mixture was stirred for 10 days at room temperature. The mixture was diluted with ethyl acetate (30 mL) and aqueous 2 N HCl (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined extracts were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1) to give **45** as a pale yellow solid (1.73 g, 74%). The diastereomeric composition (*anti*/*syn* = 8/1) was determined by

^{1}H NMR analysis of the crude product. The enantiomeric excess was determined by HPLC (Chiralpak AS-H, hexanes/2-propanol 90/10, 254 nm, t_1 = 32.6 min (minor *anti*), t_2 = 37.7 min (minor *syn*), t_3 = 53.1 min (major *syn*), t_4 = 70.5 min (major *anti*). Ee: > 99% (anti)). In repeated experiments an ee range of 97 to > 99% was observed.

IR: 3432, 3084, 2877, 2360, 2342, 1727, 1453, 1167, 1083, 1067, 1039, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.43-7.34 (m, 6H, Ar*H* and COCH=C*H*), 6.19 (dd, 1H, *J* = 5.8, 1.9 Hz, COC*H*=CH), 5.19-5.18 (br m, 1H, CH=CHC*H*), 5.09 (br t, 1H, *J* = 4.1 Hz, ArC*H*OH), 2.25 (d, 1H, *J* = 3.8 Hz, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1 (*C*=O), 152.9 (*C*H=CH-C=O), 138.3 (Ar*C*), 128.8 (Ar*C*), 128.6 (Ar*C*), 126.1 (Ar*C*), 123.2 (CH=*C*H-C=O), 86.6 (*C*H-O-C=O), 73.1 (*C*H-OH); ***Syn* diastereomer:** δ 7.42-7.36 (m, 5H, Ar*H*), 7.17 (dd, 1H, *J* = 5.8, 1.5 Hz, COCH=C*H*), 6.13 (dd, 1H, *J* = 5.8, 2 Hz, COC*H*=CH), 5.17 (apparent dt, 1H, *J* = 7.0, 1.5 Hz, CH=CHC*H*), 4.71 (d, 1H, *J* = 7.0 Hz, ArC*H*OH), 2.78 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (*C*=O), 153.0 (*C*H=CH-C=O), 137.7 (Ar*C*), 129.1 (Ar*C*), 128.8 (Ar*C*), 126.8 (Ar*C*), 123.1 (CH=*C*H-C=O), 86.9 (*C*H-O-C=O), 75.8 (*C*H-OH); MS (APCI, pos.): *m/z* 191.0 (M+1).

5-Benzylidenefuran-2(2*H*)-one (49):

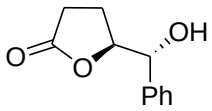


Triethylamine (292 µL, 2.10 mmol) was added slowly to an ice cold solution of **45** (200 mg, 1.05 mmol) in CH_2Cl_2, followed by the addition of methane sulfonyl chloride (122 µL, 1.57 mmol). The reaction mixture was stirred for 1 h at 0 ^{o}C and water (20 mL) was

added at 0 ^{o}C. The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 130 mg (72%) of **49** as a yellow oil.

IR: 3064, 1705, 1630, 1492, 1214, 1164, 819, 699 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl3) ***E* isomer:** δ 7.82 (1H, d, *J* = 5.6 Hz), 7.38-7.36 (5H, m), 6.80 (1H, s), 6.35 (1H, dd, *J* = 5.5, 1.8 Hz), ***Z* isomer**: δ 7.80 (2H, d, *J* = 7.4 Hz), 7.50 (1H, d, *J* = 5.3 Hz), 7.49-7.33 (3H, m), 6.23 (1H, d, *J* = 5.3 Hz), 6.04 (1H, s); MS (APCI pos.): *m/z* 192.3 (M+1).

(*S*)-Dihydro-5-[(*R*)-(hydroxy(phenyl)methyl]furan-2(3*H*)-one (45):

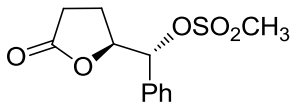


Pd/C (10%, 75 mg) was added to a stirred solution of **45** (750 mg, 3.94 mmol) in EtOAc (10.0 mL). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2. The mixture was filtered through Celite and the filter cake was washed with EtOAc (2 x 30 mL). The combined filtrates were concentrated under reduced pressure to provide 758 mg (99%) of **46** as a white solid (*syn*/*anti* = 8/1). This was pure by ^{1}H NMR and was used in the next step without purification.

IR: 3391, 1753, 1453, 1370, 1182, 1042, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.39-7.32 (m, 5H, Ar*H*), 5.13 (d, 1H, *J* = 2.7 Hz, C*H*OH), 4.72-4.65 (m, 1H, C*H*CH_2), 2.59-2.50 (m, 2H, CH_2C=O, C*H*CH_2), 2.5-2.4 (m, 1H, CH_2C=O), 2.32-2.24 (m, 1H, CH_2CH-O), 1.97-1.90 (m, 1H, CH_2CH-O); **Visible peaks for the *syn* diastereomer:** δ 4.65-4.60 (m, 1H, C*H*CH_2), 2.06-2.01 (m, 1H, CH_2CHO). ^{13}C NMR (75

MHz, $CDCl_3$): ***Anti* diastereomer:** δ 177.6 (CH_2CO), 138.4 (Ar*C*), 128.7 (Ar*C*), 128.2 (Ar*C*), 126.0 (Ar*C*), 83.3 (CH_2CHO), 73.5 (*C*HOH), 28.6 (CH_2CO), 20.7 (CH_2CHO); **Visible peaks for the *syn* diastereomer:** δ 176.8 (CH_2CO), 138.3 (Ar*C*), 128.8 (Ar*C*), 128.2 (Ar*C*), 127.0 (Ar*C*), 83.4 (CH_2CHO), 77.2 (*C*HOH), 28.5 (CH_2CO), 24.0 (CH_2CHO); MS (EI pos): *m/z*: 193.1 (M+1).

(*S*)-Dihydro-5-[(*R*)-(methylsulfonyl)(phenyl)methyl]furan-2(3*H*)-one (47):

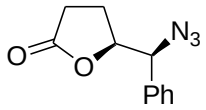


Triethyl amine (626 µL, 4.50 mmol) was added slowly to an ice cold solution of **46** (720 mg, 3.75 mmol) in CH_2Cl_2, followed by the addition of methane sulfonyl chloride (349 µL, 4.50 mmol). The reaction mixture was stirred for 1 h at 0 ^oC and water (20 mL) was added at 0 ^oC. The mixture extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 1.10 g (>99%) of **47** as a yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 3027, 2938, 1775, 1351, 1171, 1031, 944, 912, 874, 836 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.35 (m, 5H, Ar*H*), 5.73 (d, 1H, *J* = 3.9 Hz, *H*C-OSO_2Me), 4.86-4.80 (m, 1H, C*H*CH_2), 2.91 (s, 3H, C*H*$_3$), 2.50-2.40 (m, 2H, C*H*$_2$C=O), 2.28-2.09 (m, 2H, CHC*H*$_2$); **Visible peaks for the *syn* diastereomer:** δ 5.52 (d, 1H, *J* = 5.7 Hz, *H*$COSO_2Me$), 2.89 (s, 3H, C*H*$_3$); 13C NMR (75 MHz, CDCl3): ***anti***: δ 176.1, 133.5, 129.6, 129.1, 126.9, 82.8, 80.4, 39.0, 27.7, 22.1; ***syn***: δ 176.0, 133.7, 130.0, 129.2,

127.5, 84.3, 80.3, 39.3, 27.9, 24.2; MS (API-ES) *m/z* 270.4 (M^+); HRMS (CI): 271.0640 (271.0640 calc. for $C_{12}H_{15}O_5S$, M + H).

(S)-5-[(S)-Azido(phenyl)methyl]-dihydrofuran-2(3*H*)-one (48):

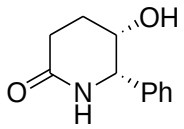


Sodium azide (1.22 g, 18.7 mmol) was added to the crude mesylate **47** (1.10 g, 4.07 mmol) in DMF (5.0 mL) and the mixture was stirred at 80 ^oC for 4 h. The mixture was cooled to room temperature and EtOAc (30 mL) was added followed by water (30 mL). The resulting biphase was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to provide 838 mg (>99%) of **48** as a yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 2101, 1774, 1455, 1250, 1175, 1148, 1066, 990, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 7.44-7.35 (m, 5H, Ar*H*), 4.71-4.61 (m, 1H, C*H*-CH_2), 4.60 (d, 1H, *J* = 5.9 Hz, C*H*N_3), 2.48-2.34 (m, 2H, CH_2C=O), 2.15-2.05 (m, 1H, CHCH_2), 2.05-1.95 (m, 1H, CHCH_2); **Visible peaks for the *anti* diastereomer:** δ 4.90 (d, 1H, *J* = 4.2 Hz, C*H*N_3), 2.58-2.45 (m, CH_2C=O), 2.25-2.15 (m, CHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 176.2 (*C*=O), 134.5 (ArC_{ipso}), 129.2 (Ar*C*), 127.8 (Ar*C*), 127.2 (Ar*C*), 81.2 (O-*C*H), 68.5 (H*C*N_3), 28.0 (*C*H_2C=O), 24.6 (*C*H_2CH); **Visible peaks for the *anti* diastereomer:** δ 176.4 (*C*=O), 134.6 (ArC_{ipso}), 129.1 (Ar*C*), 129.0 (Ar*C*),

81.4 (O-*C*H), 67.8 (H*C*N_3), 28.1 (*C*H_2C=O), 22.3 (*C*H_2CH); MS (EI pos.): m/z 218.1 (M+1); HRMS (APCI pos.): *m/z* 218.0972 (218.0930 calc. for $C_{11}H_{12}N_3O_2$ (M+H)).

(5*S*,6*S*)-5-Hydroxy-6-phenylpiperidin-2-one (22):

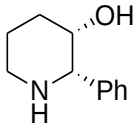


To a stirred solution of **48** (810 mg, 4.24 mmol) in methanol (5.0 mL) was added K_2CO_3 (160 mg, 1.16 mmol) followed by Pd/C (10%, 81 mg). The reaction mixture was stirred for 4 h at room temperature under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 x 30 mL) and the combined filtrates were concentrated under reduced pressure to provide a yellow gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95/5 as the eluant) to provide 543 mg (76%) of *cis*-**22** as a fluffy white solid and 91.0 mg (13 %) of *trans*-**22** as a white solid.

***Cis* diastereomer:** Mp: 99 ^oC (lit.[6b] mp. 92 ^oC); IR: 3360, 3197, 2945, 1643, 1461, 1399, 1351, 1318, 1197, 1069, 986, 942 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H, Ar*H*), 7.37-7.33 (m, 3H, Ar*H*), 5.85 (br s, 1H, CON*H*), 4.67 (d, 1H, *J* = 2.7 Hz, C*H*Ar), 4.08 (br s, 1H, C*H*OH), 2.76-2.69 (m, 1H, C*H*$_2$C=O), 2.41-2.37 (m, 1H, C*H*$_2$C=O), 2.15-2.13 (m, 1H, CHC*H*$_2$), 2.04-2.01 (m, 1H, CHC*H*$_2$), 1.69 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (*C*=O), 137.9 (Ar*C*$_{ipso}$), 129.2 (Ar*C*), 128.7 (Ar*C*), 127.0 (Ar*C*), 66.2 (*C*HOH), 61.9 (*C*HAr), 26.7 (CH*C*H$_2$), 26.07 (*C*H$_2$C=O); MS (APCI, pos.) *m/z* 192.1 (M+1); HRMS (EI): 191.0950 (191.0946 calc. for $C_{11}H_{13}NO_2$ (M+H)); $[\alpha]_D^{23}$ = +55.3 (*c* 1.06, CH_2Cl_2), lit. $[\alpha]_D^{25}$ = +52.0 (*c* 1.1, CH_2Cl_2).[6b]

***Trans* diastereomer**: IR: 3237, 2364, 1631, 1581, 1485, 1446, 1349, 1333, 1175, 1076, 945, 801 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45-7.40 (m, 2H, Ar*H*), 7.40-7.35 (m, 3H, Ar*H*), 5.70 (br s, 1H, CON*H*), 4.69 (d, *J* = 2.8 Hz, 1H, C*H*Ar), 4.10 (br s, 1H, C*H*OH), 2.77 (ddd, 1H, *J* = 18.0, 11.9, 6.5 Hz, CH_2CO), 2.43 (ddd, 1H, *J* = 18.0, 6.2, 2.8 Hz, CH_2CO), 2.19-2.15 (m, 1H, CHCH_2), 2.07-2.03 (m, 1H, CHCH_2), 1.47 (br t, 1H, *J* = 1.5 Hz, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (*C*=O), 137.8 (ArC_{ipso}), 129.2 (Ar*C*), 128.8 (Ar*C*), 127.0 (Ar*C*), 66.3 (*C*HOH), 61.9 (*C*HAr), 26.7 (CH*C*H_2), 26.1 (*C*H_2C=O); MS (APCI pos.): *m/z* 192.3 (M^+); $[\alpha]_D^{23}$ = +26.0 (*c* 1.0 , MeOH); lit. $[\alpha]_D^{23}$ = +31.6 (*c* 0.75, MeOH).[18]

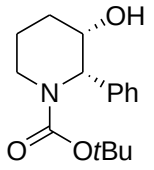
(2*S*,3*S*)-2-Phenylpiperidin-3-ol (50):



Borane-THF complex (4.70 mL, 4.68 mmol) was added to *cis*-**22** (300 mg, 1.56 mmol), and the mixture was heated to reflux for 5 h. The mixture was cooled to 0 ^oC, aqueous HCl (3 M, 12.0 mL) was added and the mixture was stirred for 30 min. at room temperature. The mixture was then concentrated to dryness under reduced pressure and the residue was basified with 5% aqueous NaOH at 0 ^oC to pH~10. The resulting mixture was extracted with EtOAc, dried (Na_2SO_4) and concentrated to provide **50** as a white solid (267 mg, 96%). This was pure by ^1H NMR and was used in the next step without purification.

Mp: 90-93 ^{o}C; IR: 3274, 2926, 2851, 1447, 1323, 1089, 1054, 1053, 989 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H, Ar*H*), 7.32-7.24 (m, 2H, Ar*H*), 3.86 (br s, 1H, C*H*Ar), 3.78 (br s, 1H, C*H*OH), 3.22-3.19 (m, 1H, NCH_2), 2.81 (dt, 1H, *J* = 12.1, 2.8 Hz, NCH_2), 2.02-1.92 (m, 1H, CHCH_2), 1.89-1.84 (m, 1H, CHCH_2), 1.74-1.67 (m, 1H, CH_2CH_2N), 1.52-1.48 (m, 1H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0 (ArC_{ipso}), 128.5 (Ar*C*), 127.3 (Ar*C*), 126.6 (Ar*C*), 68.9 (*C*HOH), 65.0 (*C*HAr), 47.5 (N*C*H_2), 32.0 (CH*C*H_2), 19.9 (*C*H_2CH_2N); MS (APCI, pos.): *m/z* 178.1 (M+1); HRMS (EI): 177.1153 (177.1154 calcd for $C_{11}H_{15}NO$); $[\alpha]_D^{23}$ = +66.45 (*c* 0.62, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (13):

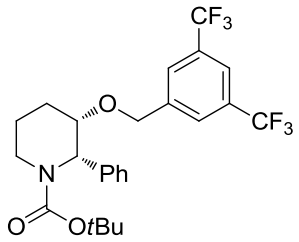


To a solution of **50** (500 mg, 2.82 mmol) in CH_2Cl_2 (5.0 mL) were added di-*tert*-butyl dicarbonate (616 mg, 2.82 mmol), 4-(dimethylamino)pyridine (25 mg, 0.20 mmol) and triethylamine (431 µL, 3.10 mmol) at 0 ^{o}C. The solution was stirred at room temperature for 3 h, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 7/3) afforded 663 mg (85%) of **13** as colorless oil.

IR: 3452, 2937, 1661, 1413, 1362, 1255, 1175, 1141, 1074, 1024, 962, 871 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 7.45 (d, 2H, *J* = 7.6 Hz, Ar*H*), 7.34 (t, 2H, *J* = 7.6 Hz, Ar*H*),

7.28-7.26 (m, 1H, Ar*H*), 5.33 (d, 1H, *J* = 5.4 Hz, C*H*Ar), 4.1-4.06 (m, 1H, C*H*OH), 4.01 (dd, *J* = 4.9 Hz, 13.2 Hz, 1H, NCH_2), 3.04 (dt, *J* = 3.9 Hz, 13.2, 1H, NCH_2), 1.84-1.67 (m, 3H, CH_2CH_2), 1.67-1.62 (m, 1H, CH_2CH_2), 1.58 (s, 1H, O*H*), 1.37 (s, 9H, C(CH_3)$_3$) ; ^{13}C NMR (500MHz, $CDCl_3$): δ 155.4 (*C*=O), 138.4 (ArC_{ipso}), 128.4 (Ar*C*), 127.2 (Ar*C*), 79.9 (*C*(CH$_3$)$_3$), 70.1 (*C*HOH), 59.3 (*C*HAr), 39.5 (*C*H$_2$N), 28.3 ((*C*H$_3$)$_3$, 27.7 (CH*C*H$_2$), 23.1 (NCH_2CH_2); MS (APCI, pos.): *m/z* 178.1 ((M-Boc)+1); $[\alpha]_D^{23}$ = +42.3 (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{24}$ = +42.6 (*c* 0.54, $CHCl_3$).[6b]

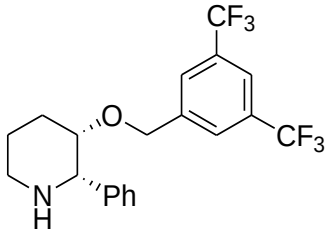
(2*S*,3*S*)-*tert*-Butyl-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-phenylpiperidine-1-carboxylate (13a):



To a solution of **13** (60 mg, 0.22 mmol) in DMF/THF (3:1, 1.0 mL) under N_2 at 0 ^oC was added sodium hydride (95%, 16 mg, 0.65 mmol). The mixture was stirred at room temperature for 30 min. and 3,5-bis(trifluoromethyl)benzyl bromide (0.10 g, 0.33 mmol) was added at 0 ^oC. The mixture was stirred 16 h at room temperature, after which water (5.0 mL) added at 0 ^oC and the mixture was extracted with Et_2O (2 x 10 mL) The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 9/1) to give 57 mg (52%) of **13a** as colorless oil.

IR: 2939, 1686, 1411, 1357, 1276, 1175, 1128, 885 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 7.77 (s, 1H, Ar*H*), 7.71 (s, 2H, Ar*H*), 7.55 (d, 2H, *J* = 7.7 Hz, Ar*H*), 7.33 (t, 2H, *J* = 7.7 Hz, Ar*H*), 7.27-7.25 (m, 1H, Ar*H*), 5.69 (br s, 1H, C*H*Ar), 4.73 (AB system, 2H, *J* = 12.6 Hz, CH_2Ar), 3.96-3.90 (m, 1H, NCH_2 or C*H*O), 3.90-3.86 (m, 1H, NCH_2 or C*H*O), 2.77 (dt, *J* = 13.1, 3.2 Hz, 1H, NCH_2), 2.01-1.96 (m, 2H, CHCH_2), 1.74-1.70 (m, 1H, CH_2CH_2N), 1.70-1.60 (m, 1H, CH_2CH_2N), 1.46 (s, 9H, C(CH_3)$_3$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3 (*C*=O), 141.0 (Ar*C*), 138.01 (Ar*C*), 131.6 (q, *J* = 33.3 Hz, *C*F_3), 128.4 (Ar*C*), 128.3 (Ar*C*), 127.2 (br, Ar*C*), 127.1 (Ar*C*), 125.1 (Ar*C*), 121.5-121.4 (br, Ar*C*), 80.1 (*C*(CH_3)$_3$), 78.7 (*C*H-O), 69.2 (*C*H_2Ar), 55.5 (*C*HAr), 39.2 (N*C*H_2), 28.4 (C(*C*H_3)$_3$), 25.9 (CH*C*H_2), 24.2 (*C*H_2CH_2N); MS (APCI, pos.): *m/z* 404.2 ((M-Boc)+1); $[\alpha]_D^{23}$ = +39.1 (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{25}$ = +27.9 (*c* 0.8, $CHCl_3$).[6e]

(2*S*,3*S*)-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-phenylpiperidine ((+)-L-733,060):

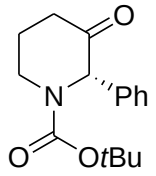


To a solution **13a** (46 mg, 0.09 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (70 µL, 0.91 mmol) at 0 ^{o}C. The mixture was stirred at room temperature for 18 h and 10% aqueous NaOH was added at 0 ^{o}C. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to

afford 34 mg (92%) of (+)-L-733,060 as a colorless oil that was pure by ^{1}H NMR (500 MHz).

IR: 2936, 2858, 1374, 1342, 1276, 1174, 1126, 883, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 7.69 (s, 1H, Ar*H*), 7.44 (s, 2H, Ar*H*), 7.37 (br d, 2H, *J* = 7.3 Hz, Ar*H*), 7.32 (br t, *J* = 7.2 Hz, 2H, Ar*H*), 7.27 (m, 1H, Ar*H*), 4.52 (d, 1H, *J* = 12.5 Hz, C*H*$_2$Ar), 4.14 (d, 1H, *J* = 12.5 Hz, C*H*$_2$Ar), 3.85 (s, 1H, C*H*Ar), 3.68 (s, 1H, C*H*OCH$_2$Ar), 3.30-3.27 (m, 1H, NC*H*$_2$), 2.85 (dt, *J* = 12.4, 2.8 Hz, 1H, NC*H*$_2$), 2.22 (d, 1H, *J* = 13.9 Hz, CHC*H*$_2$), 1.89-1.82 (m, 1H, CHC*H*$_2$), 1.77-1.70 (m, 1H, C*H*$_2$CH$_2$CH-O), 1.54-1.51 (m, 1H, C*H*$_2$CH$_2$CH-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4 (Ar*C*), 141.1 (Ar*C*), 131.33 (q, *J* = 33.2 Hz, *C*F$_3$), 128.2 (Ar*C*), 127.5 (Ar*C*), 127.3 (Ar*C*), 126.8 (Ar*C*), 125.1 (Ar*C*), 121.5-121.2 (m, Ar*C*), 77.1 (*C*H-O), 70.1 (*C*H$_2$Ar), 64.2 (*C*HAr), 46.9 (N*C*H$_2$), 28.4 (*C*H$_2$CH-O), 20.3 (*C*H$_2$CH$_2$N); MS (APCI pos.): *m/z* 404.4 (M^{+}); HRMS (CI): *m/z* 404.1447 (404.1449 calcd for $C_{20}H_{20}F_6NO$, M+H); $[\alpha]_D^{23}$ = +48.6 (*c* 0.51, $CHCl_3$); lit. $[\alpha]_D^{24}$ = +31.7 (*c* 0.5, $CHCl_3$)[6e].

(*S*)-*tert*-Butyl-3-oxo-2-phenylpiperidine-1-carboxylate (12):

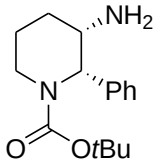


Dess-Martin periodinane (1.07 g, 2.50 mmoles) was added to a solution of alcohol **13** (0.14 g, 0.50 mmol) in CH_2Cl_2 (3.0 mL) and the mixture was stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added, the organic layer was

separated and the aqueous layer was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 8/2) to give 106 mg (76%) of **12** as a pale yellow liquid.

IR: 2974, 1690, 1401, 1361, 1247, 1154 (br), 1105, 1031, 967 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.37-7.20 (m, 5H, Ar*H*), 5.65 (br s, 1H, C*H*Ar), 4.08 (br s, 1H, CH_2N), 3.34-3.30 (br m, 1H, CH_2N), 2.51-2.40 (m, 2H, CH_2C=O), 1.98-1.88 (m, 2H, CH_2CH_2C=O), 1.43 (br s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (CH_2C=O), 155.0 (N-*C*=O), 135.6 (Ar*C*), 128.9 (Ar*C*), 127.6 (Ar*C*), 125.4 (Ar*C*), 80.7 (*C*(CH_3)$_3$), 65.9 (br, *C*HAr), 40.1 (br, N*C*H_2), 37.3 (*C*H_2C=O), 28.2 (C(*C*H_3)$_3$), 22.8 (*C*H_2CH_2N); HRMS (EI pos.): 275.1525 (275.1521 calcd for $C_{16}H_{21}NO_3$); HPLC: Chiralpak AD-H, hexanes/2-propanol 99/1, 254 nm, t_{major} = 35.7 min, t_{minor} = 37.6 min.; ee = 96% ee.

(2*S*,3*S*)-*tert*-Butyl 3-amino-2-phenylpiperidine-1-carboxylate (51):

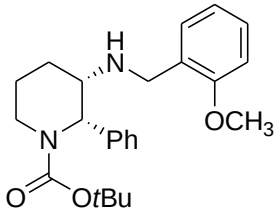


To a stirred solution of ketone **12** (60 mg, 0.22 mmoles) in ethanol (0.50 mL) at room temperature, was added anhydrous pyridine (26 μL, 0.33 mmol) followed by methoxylamine hydrochloride (27 mg, 0.33 mmol) and the mixture was stirred at room temperature for 30 min. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was stirred for 30 min, and then extracted with diethyl ether (3 x 30 mL). The combined

organic layers were dried (Na_2SO_4), and concentrated to provide the crude oxime methyl ether of **51** (70 mg). This was treated with BH_3-THF (1 M soln. in THF, 0.65 mL, 0.63 mmoles) under N_2 and the solution was stirred at 50 ^oC for 4h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 30 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 9/1) to provide 40 mg (67%) of **51** as pale yellow oil. This was pure by ^1H NMR and was used in the next step without purification.

IR: 2931, 1682, 1407, 1362, 1252, 1147, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.44 (d, 2H, *J* = 7.3 Hz, Ar*H*), 7.31-7.28 (m, 2H, Ar*H*), 7.26-7.23 (m, 1H, Ar*H*), 5.20 (d, 1H, *J* = 6.0 Hz, C*H*Ar), 4.01 (br d, 1H, *J* = 10.9 Hz, C*H*NH_2), 3.20-3.11 (m, 2H, NCH_2), 1.88-1.65 (m, 4H, CH_2CH_2CH), 1.45 (br s, 2H, NH_2), 1.36 (s, 9H, C(CH_3)$_3$); 13C NMR (75 MHz, CDCl3): δ 155.4 (*C*$O_2{}^t$Bu), 139.1 (Ar*C*), 129.4 (2 × Ar*C*), 128.2 (2 × Ar*C*), 127.2 (Ar*C*), 79.7 (O*C*$(CH_3)_3$), 60.6 (N*C*H), 51.2 (*C*HNH_2), 39.8 (N*C*H_2), 29.2 (NH_2CH*C*H_2), 28.3 (C(*C*$H_3)_3$), 24.4 (NCH_2*C*H_2); MS (EI pos.): *m/z* 277.2 (M + 1).

(2*S*,3*S*)-*tert*-Butyl 3-(2-methoxybenzylamino)-2-phenylpiperidine-1-carboxylate (51a):

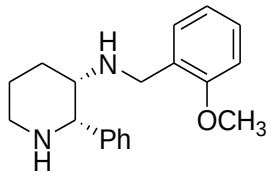


To a solution of amine **51** (16 mg, 0.06 mmol) in THF (1.0 mL) was added 2-methoxybenzaldehyde (21 μL, 0.17 mmol) and the mixture was stirred at room

temperature for 22 h. The solvent was removed under reduced pressure and the residue was dissolved in methanol (1.0 mL). Sodium borohydride (13 mg, 0.35 mmoles) was added to this solution and the mixture was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (pH~8) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/ EtOAc, 9/1) to provide 18 mg (78%) of **51a** as pale yellow oil. This was pure by ^{1}H NMR and was used in the next step without purification.

IR: 2933, 1685, 1494, 1457, 1407, 1359, 1241, 1178, 1144, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 2H, *J* = 7.3 Hz, Ar*H*), 7.33-7.28 (m, 2H, Ar*H*), 7.26-7.18 (m, 3H, Ar*H*), 6.89 (t, 1H, *J* = 7.4 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.5 Hz, Ar*H*), 5.47 (s, 1H, C*H*Ar), 3.95 (d, 1H, *J* = 11.1 Hz, NCH_2), 3.77 (AB system, 2H, *J* = 13.4 Hz, CH_2Ar), 3.71 (s, 3H, OCH_3), 3.07-3.03 (m, 1H, C*H*NH), 2.97 (dt, 1H, *J* = 13.0, 2.3 Hz, NCH_2), 1.85-1.75 (m, 3H, CH_2CHN*H*), 1.66-1.53 (m, 2H, CH_2CH_2N), 1.41 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (*C*O), 155.2 (Ar*C*), 139.2 (Ar*C*), 129.5 (Ar*C*), 129.2 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 126.9 (Ar*C*), 120.4 (Ar*C*), 110.1 (Ar*C*), 79.6 (*C*(CH_3)$_3$), 57.2 (*C*HAr), 55.0 (*C*HNH, O*C*H_3), 46.6 (*C*H_2Ar), 39.5 (N*C*H_2), 28.4 (C(*C*H_3)$_3$, 26.8 (*C*H_2CHNH), 24.3 (*C*H_2CH_2N); MS (EI pos.): *m/z* 397.5 (M+1); HRMS (EI): *m/z* 396.2412 (396.2413 calcd for $C_{24}H_{32}N_2O_3$); HPLC (Chiralpak OD-H, hexanes/2-propanol 90/10, 210 nm, t_{minor} = 4.64 min, t_{major} = 5.20 min; ee = 93.4%.

(2*S*,3*S*)-*N*-(2-Methoxybenzyl)-2-phenylpiperidin-3-amine ((+)-CP-99,994):

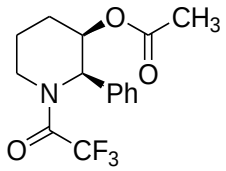


To a solution of **51a** (18 mg, 0.05 mmol) in MeOH (0.50 mL) was added 1:1 mixture of conc. aqueous HCl and methanol (1.0 mL) at 0 ^{o}C and the mixture was stirred at room temperature for 22 h. Saturated aqueous $NaHCO_3$ was added (pH~8), and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4), and concentrated to give 12 mg (92%) of CP-99,994 as a pale yellow oil that was pure by ^{1}H NMR (500 MHz).

IR: 2935, 2846, 1647, 1595, 1492, 1451, 1239, 1111, 1027, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.12 (m, 6H, Ar*H*), 6.97 (d, 1H, *J* = 7.3 Hz, Ar*H*), 6.80 (t, 1H, *J* = 7.3 Hz, Ar*H*), 6.67 (d, *J* = 8.2 Hz, 1H, Ar*H*), 3.87 (s, 1H, C*H*Ar), 3.67 (d, 1H, *J* = 13.9 Hz, CH_2Ar), 3.44 (s, 3H, OCH_3), 3.41 (d, 1H, *J* = 13.9 Hz, CH_2Ar), 3.28-3.25 (m, 1H, C*H*NH), 2.82-2.76 (m, 2H, NCH_2), 2.14 (br d, 1H, *J* = 13.5 Hz, CH_2CHNH), 1.95-1.91 (m, 1H, CH_2CH$_2$NH), 1.77 (br s, 2H, N*H*), 1.63-1.57 (m, 1H, CH_2CHNH), 1.39 (br d, 1H, *J* = 13.1 Hz, CH_2CH$_2$NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (Ar*C*), 142.4 (Ar*C*), 129.5 (Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 127.8 (Ar*C*), 126.5 (Ar*C*), 126.3 (Ar*C*), 119.9 (Ar*C*), 109.7 (Ar*C*), 63.9 (*C*HAr), 54.7 (N*C*H), 54.6 (OCH_3), 47.7 (*C*H_2Ar), 46.7 (N*C*H_2), 28.2 (*C*H_2CHN), 20.3 (*C*H_2CH$_2$NH); MS (APCI pos.): *m/z*: 297.4 (M+1); HRMS (EI): 296.1898 (296.1889 calcd for $C_{19}H_{24}N_2O$, M^+); $[\alpha]_D^{23}$ = +68.0 (*c* 1.1,

$CHCl_3$); lit. $[\alpha]_D^{20}$ = +67.2 (*c* 1, $CHCl_3$);[13] HPLC (Chiralpak OD-H, hexanes/2-propanol 90/10, 210 nm, t_{major} = 6.07 min, t_{minor} = 8.94 min; ee = 94.8%.

_N_-Trifluoroacetyl-(2*S*,3*R*)-3-acetoxy-2-phenylpiperidine (53):

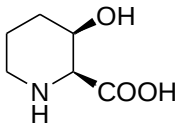


To an ice cold solution of the aminoalcohol **52** (*ent*-**50**, 500 mg, 2.82 mmol; prepared as described for **50**, but with the enantiomer of catalyst **44**) in CH_2Cl_2 (30.0 mL) containing Et_3N (2.30 mL, 16.9 mmol) and 4-(dimethylamino)pyridine (17 mg, 0.14 mmol) was added triflouroacetic anhydride (1.60 mL, 11.3 mmol). The solution was stirred at room temperature for 12 h, water was added and the solution was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4), and concentrated. The residue was dissolved in THF (30.0 mL), K_2CO_3 (770 mg, 5.57 mmol) was added and the mixture was stirred for 36 h at room temperature. Water was added and the mixture was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 7/3) to provide 715 mg (93%) of the trifluoroacetamide derivative of **52**. This was dissolved in CH_2Cl_2 (30.0 mL), Et_3N (1.57 mL, 11.3 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol) were added and the solution was cooled to 0 ^oC. Acetic anhydride (530 μL, 5.19 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and

concentrated. The crude product was purified by flash chromatography (hexanes/ EtOAc, 8/2) to provide 795 mg (89%) of **53** as a pale yellow oil.

IR: 1743, 1687, 1451, 1370, 1235, 1193, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**: Major rotamer:** δ 7.49-7.26 (m, 5H, Ar*H*), 5.99 (d, 1H, *J* = 5.7 Hz, C*H*Ar), 5.25-5.20 (m, 1H, C*H*OAc), 3.83 (br d, 1H, *J* = 14.0 Hz, NCH_2), 3.19-3.13 (m, 1H, NCH_2), 2.17-2.11 (m, 2H, CH_2CHOAc), 2.0 (s, 3H, COCH_3), 1.85-1.83 (m, 2H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*OCH_3), 135.4 (*C*OCF_3), 128.9 (Ar*C*), 128.7 (Ar*C*), 128.0 (Ar*C*), 128.0 (Ar*C*), 127.8 (Ar*C*), 116.6 (q, *J* = 288.0 Hz, CF_3), 55.5(*C*HAr), 41.2 (q, *J* = 3.4 Hz, *C*H_2N), 24.9 (*C*H_2CH-O), 23.9 (*C*H_3), 21.1 (*C*H_2CH_2N); **Minor rotamer:** ^{1}H NMR (500 MHz, $CDCl_3$)**,** visible peaks: 5.55 (d, *J* = 5.3 Hz, 1H, C*H*Ar), 4.37 (d, *J* = 11.8 Hz, 1H, CH_2N), 2.75 (dt, 1H, *J* = 13.3, 4.1 Hz, NCH_2N). ^{13}C NMR (75 MHz, $CDCl_3$), visible peaks: δ 169.7 (*C*OCH_3), 156.5 (q, *J* = 36.1 Hz, *C*F_3), 135.0 (*C*OCF_3), 72.4 (*C*H-O), 70.6 (*C*HO), 57.7 (*C*HAr), 38.8 (*C*H_2CH-O), 23.5 (*C*H_3), 21.1 (*C*H_2CH_2N); MS (APCI pos.): *m/z* 316.1 (M+1).

(2*R*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid:



To a mixture of **53** (0.15 g, 0.48 mmol) in carbon tetrachloride (0.75 mL), acetonitrile (0.75) mL and water (1.1 mL), were added sodium periodate (1.53 g, 7.13 mmol) and ruthenium chloride (5.0 mg, 0.02 mmol) and the mixture was stirred vigorously at ambient temperature for 20 h. The mixture was filtered through a pad of Celite and the

residue was rinsed several times with CH_2Cl_2. The black filtrates were combined, dried (Na_2SO_4) and concentrated. The residue obtained was dissolved in methanol (5.0 mL), K_2CO_3 (393 mg, 2.84 mmol) was added and the mixture was stirred at room temperature for 12 h. The resulting solution was concentrated and the residue was dissolved in aqueous 1 N HCl (1.0 mL). This solution was applied to a column of Dowex 50Wx8 resin (200-400 dry mesh) and the column was eluted with deionized water (250 mL) followed by 5% aqueous ammonia. The ninhydrin positive fractions were combined and concentrated to provide 40 mg (58%) of (2*R*,3*R*)-3-hydroxypiperidine-2-carboxylic acid as a white solid.

Mp. 231-235 ^{o}C (lit.[8a] mp 233-238 ^{o}C); IR: 3600-2859 (br), 1618 (br), 1461, 1399, 1312, 1205, 1137, 1083, 1042, 996 cm^{-1}; ^{1}H NMR (500 MHz, D_2O)**:** δ 4.44 (s, 1H, C*H*COOH), 3.60 (d, 1H, *J* = 1.4 Hz, C*H*-OH), 3.37-3.33 (m, 1H, CH_2NH), 2.94 (dt, 1H, *J* = 3.5, 12.9 Hz, CH_2NH), 1.95-1.84 (m, 2H, CH_2CHOH), 1.76-1.66 (m, 2H, CH_2CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (*C*OOH), 64.1 (*C*H-OH), 62.2 (*C*HCOOH), 43.6 (*C*H_2N), 28.7 (*C*H_2CHOH), 15.9 (*C*H_2CH_2N); MS (APCI pos.): *m/z* 146.1 (M+H); $[\alpha]_D^{23}$ = -53.5 (*c* 0.6, H_2O); lit. $[\alpha]_D^{24}$ = - 52.8 (*c* 0.6, H_2O). [8f]

3.6 References

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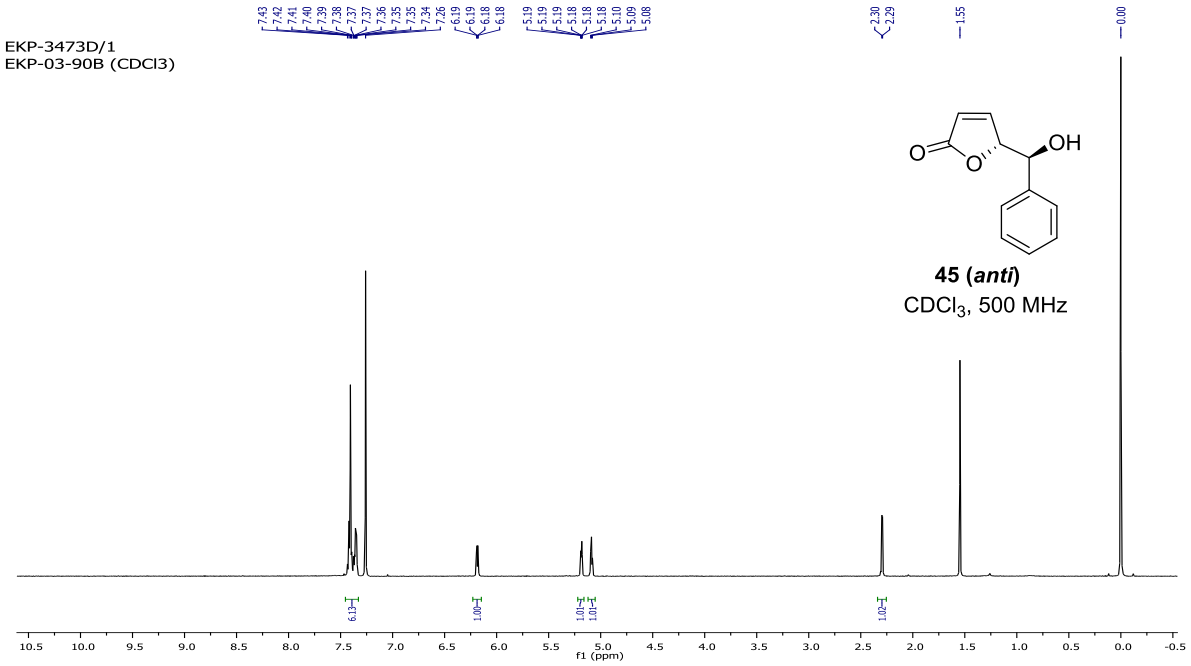
3.7 Selected ^{1}H and ^{13}C NMR spectra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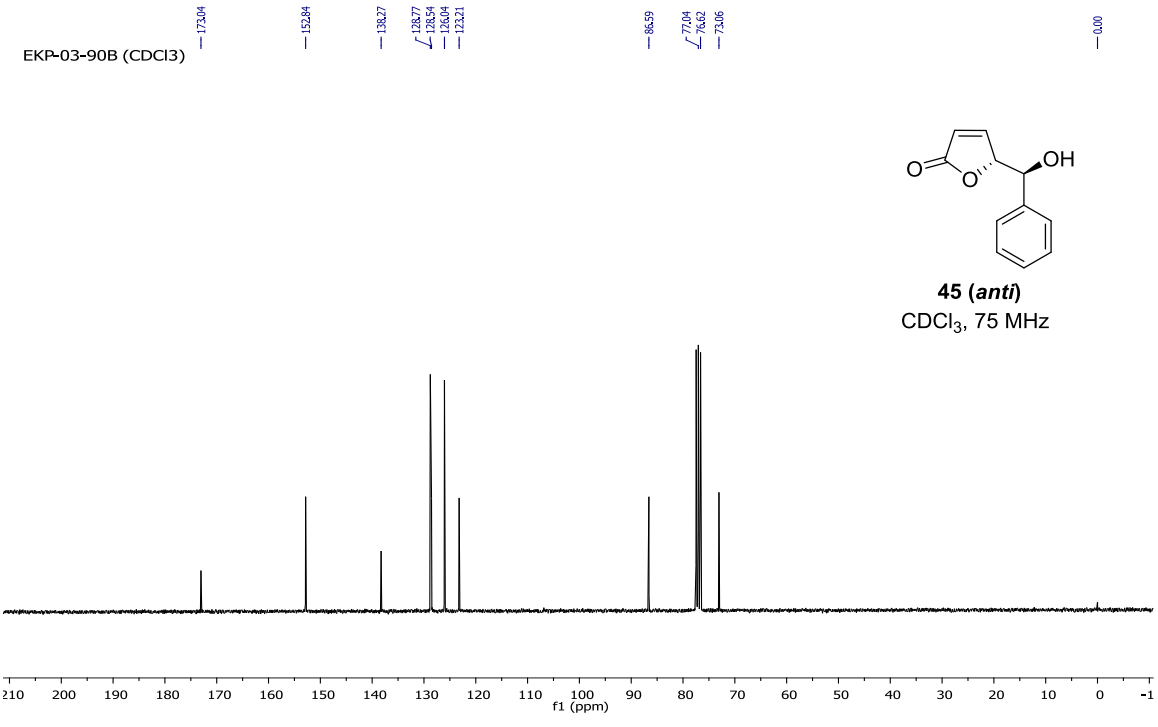
7.36
7.35
7.35
7.24
7.26
6.19
6.19
6.18
6.18
5.19
5.19
5.19
5.18
5.18
5.18
5.10
5.09
5.08
2.30
2.29
1.55
0.00
O
O
OH
45 (anti)
CDCl3, 500 MHz
6.13
1.00
1.01
1.01
1.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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76.62
73.06
0.00
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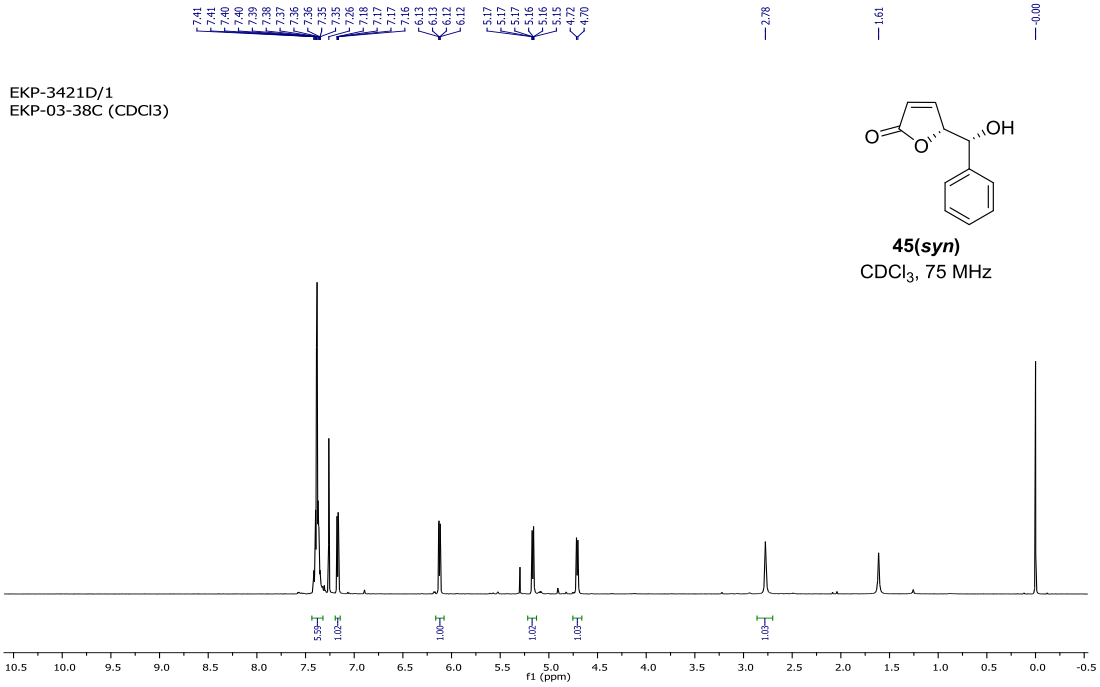
O
OH
45 (anti)
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)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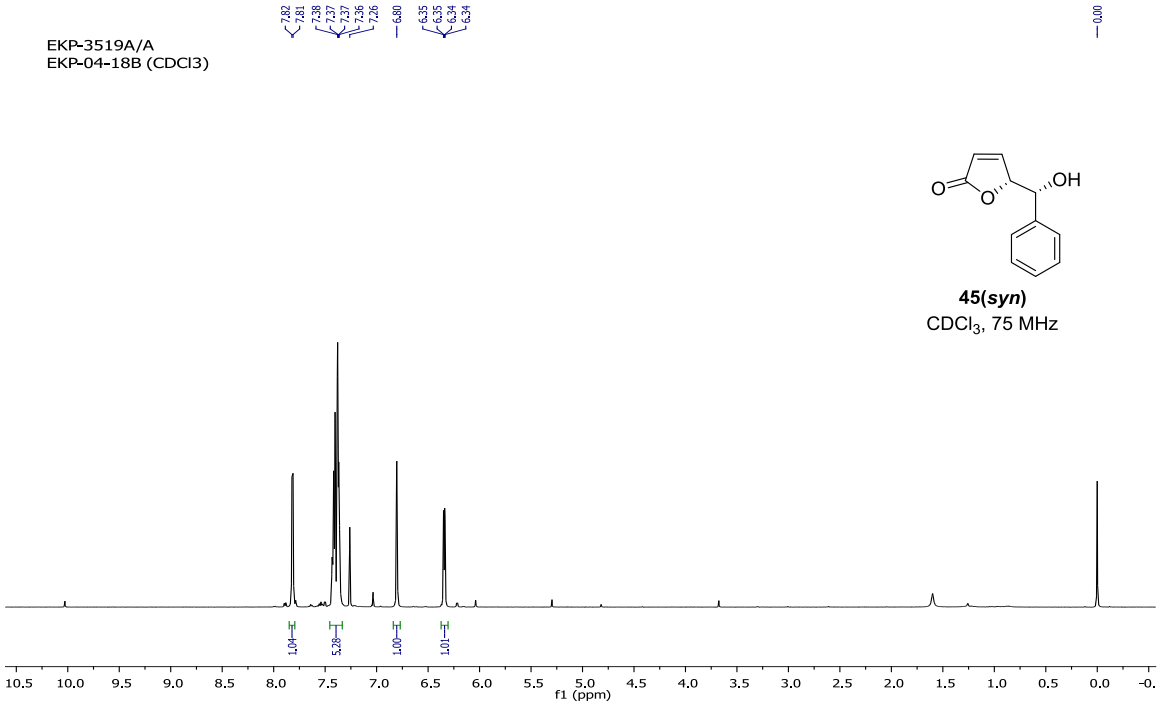
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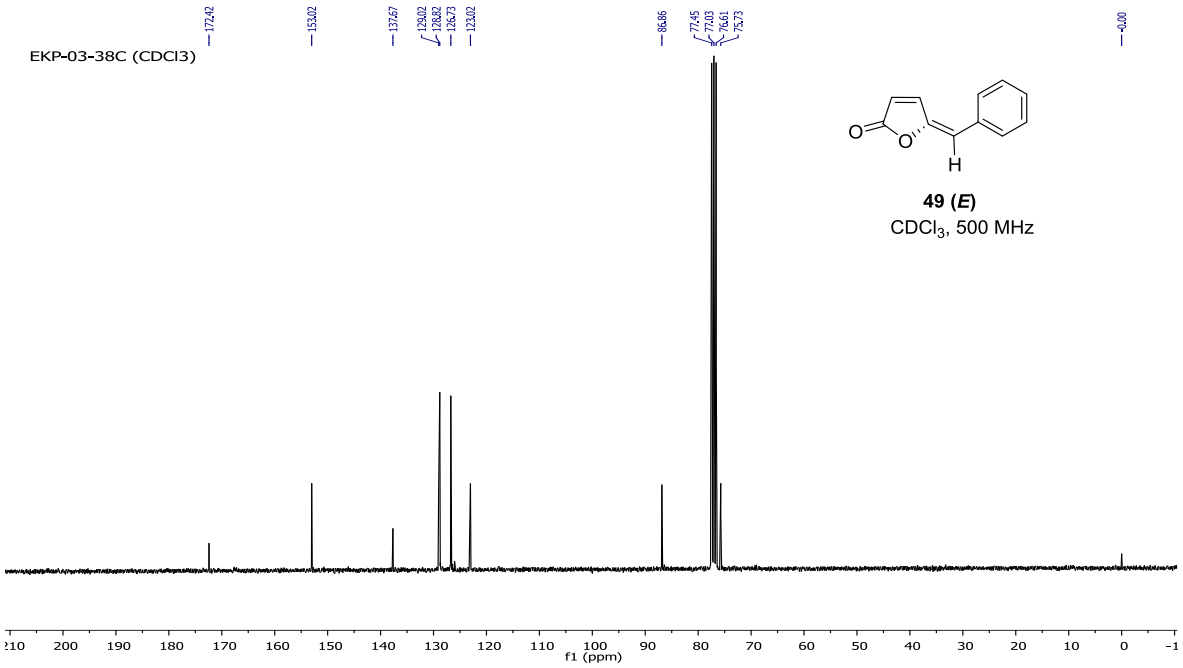
O
45(syn)
CDCl3, 75 MHz
f1 (ppm)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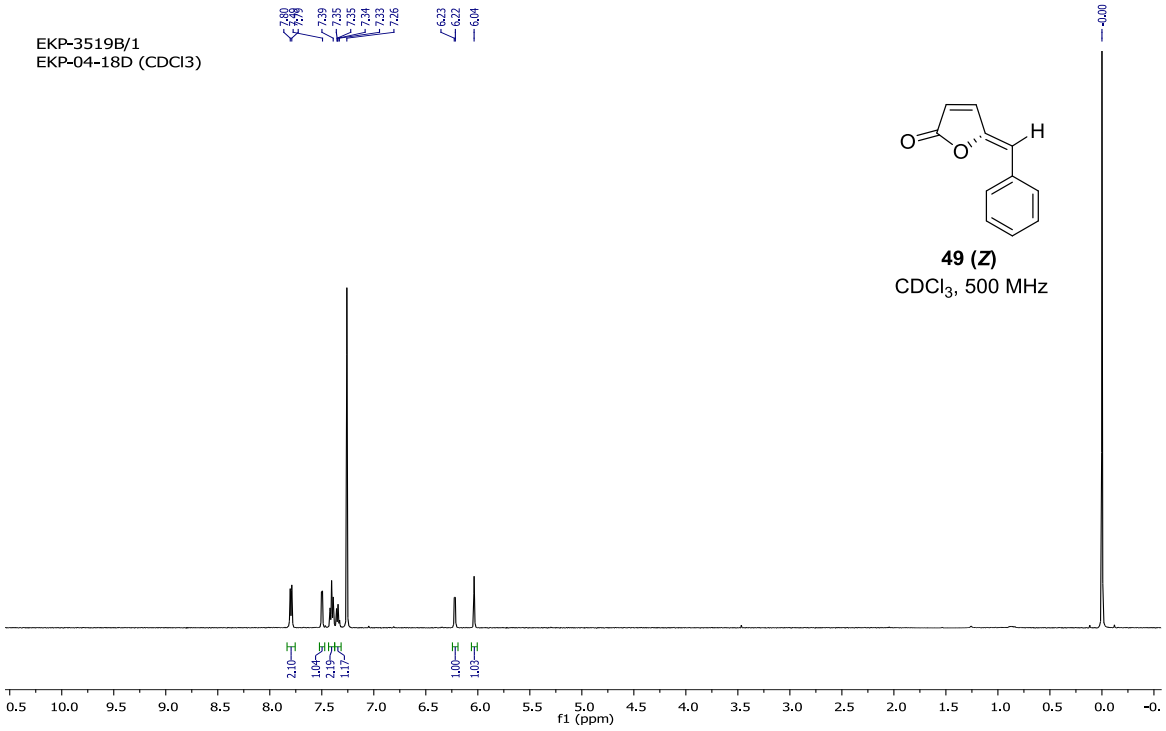
O
O
H
49 (E)
CDCl3, 500 MHz
f1 (ppm)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7.26
6.23
6.22
6.04
0.00
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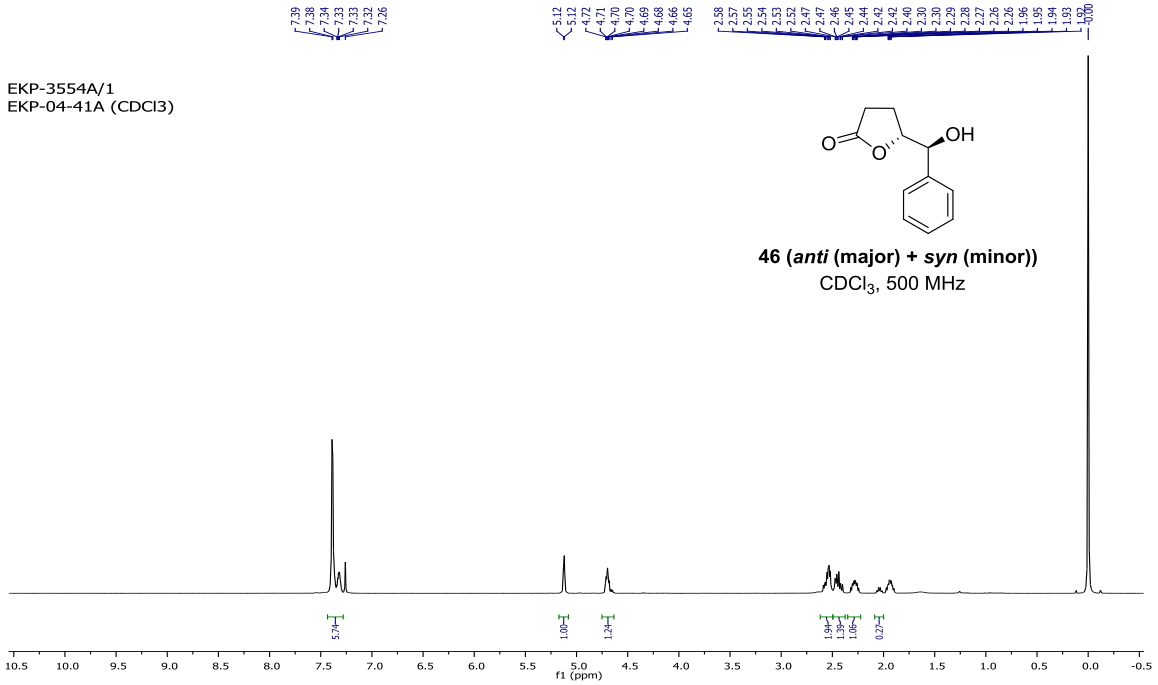
O
H
49 (Z)
CDCl3, 500 MHz
f1 (ppm)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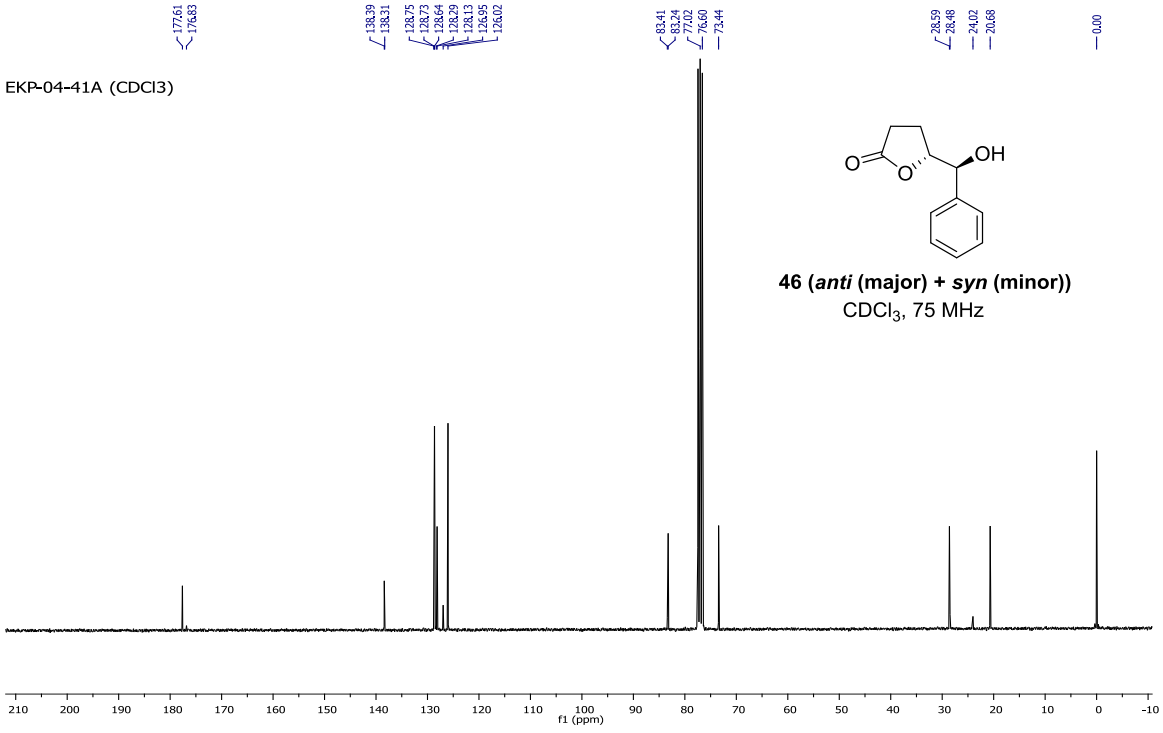
f1 (ppm)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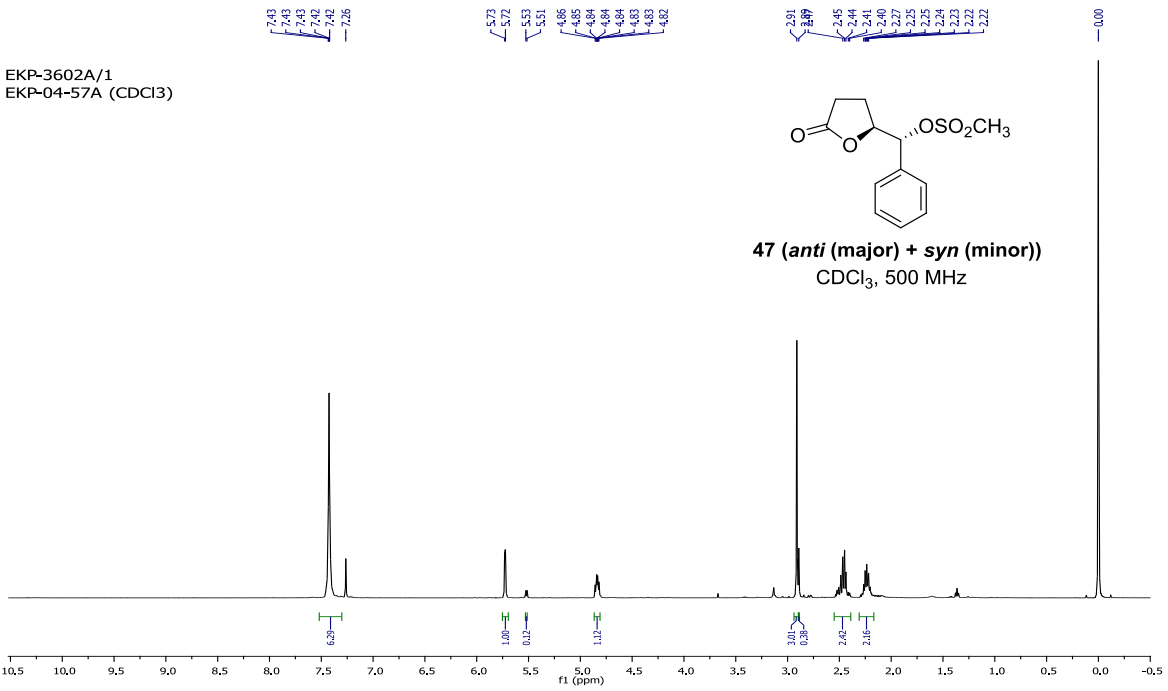
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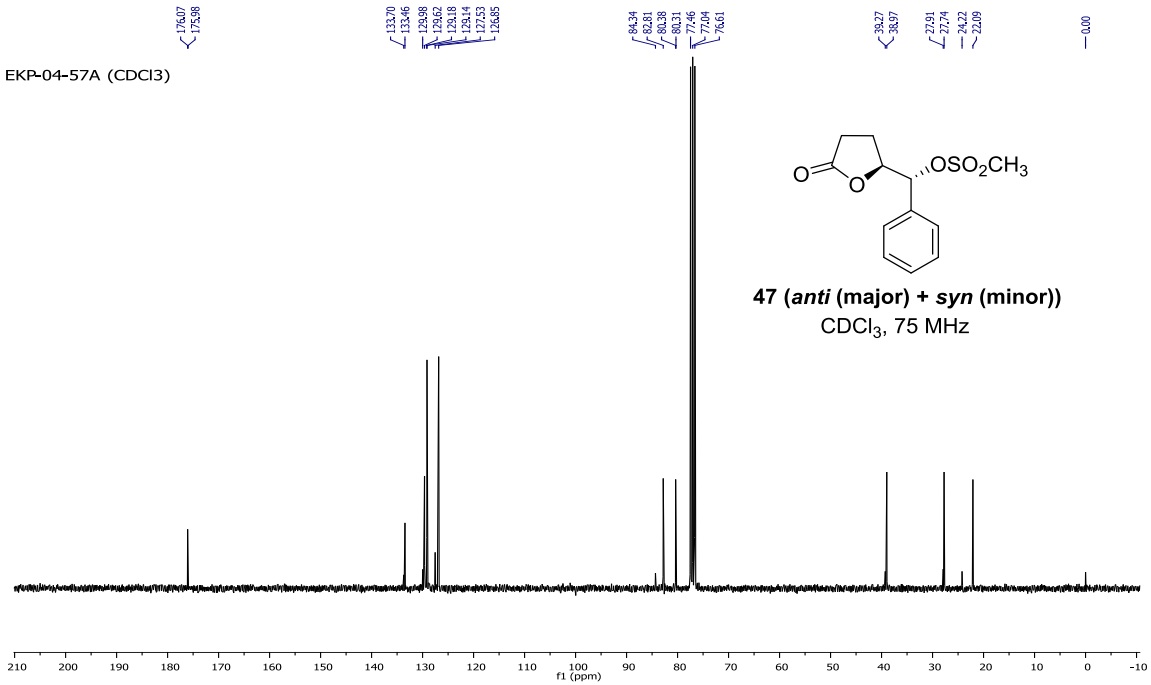
f1 (ppm)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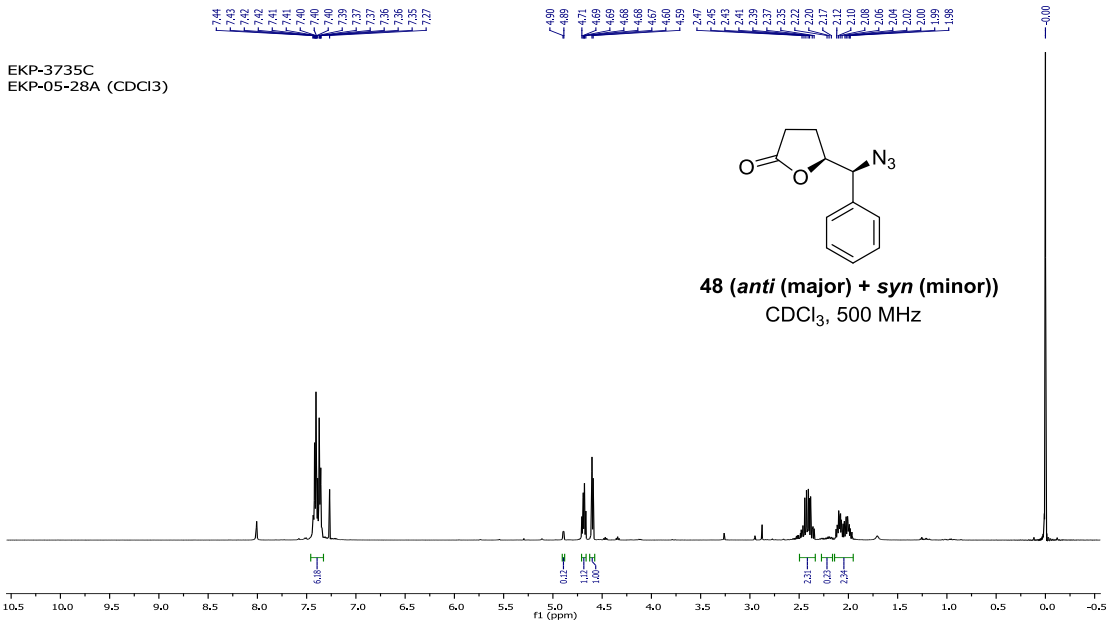
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N3
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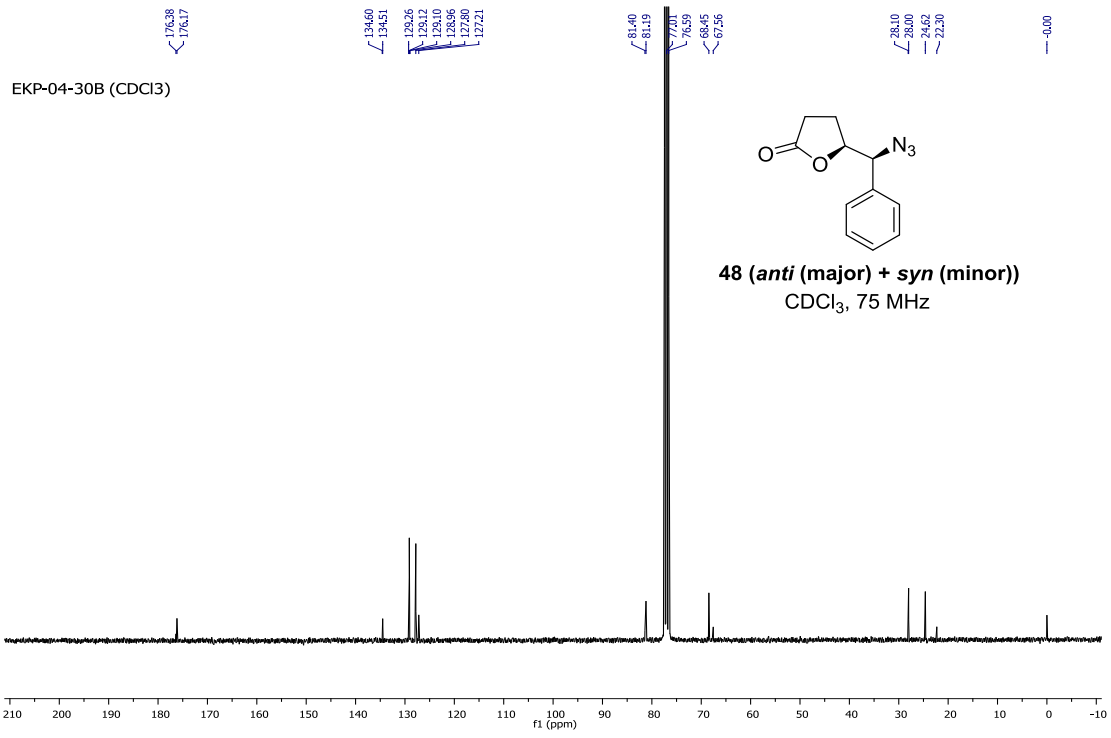
f1 (ppm)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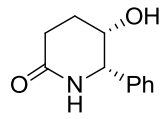

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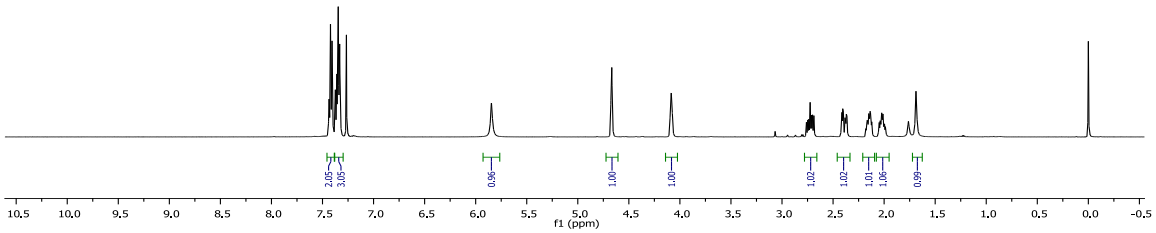

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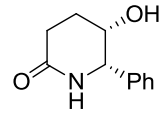

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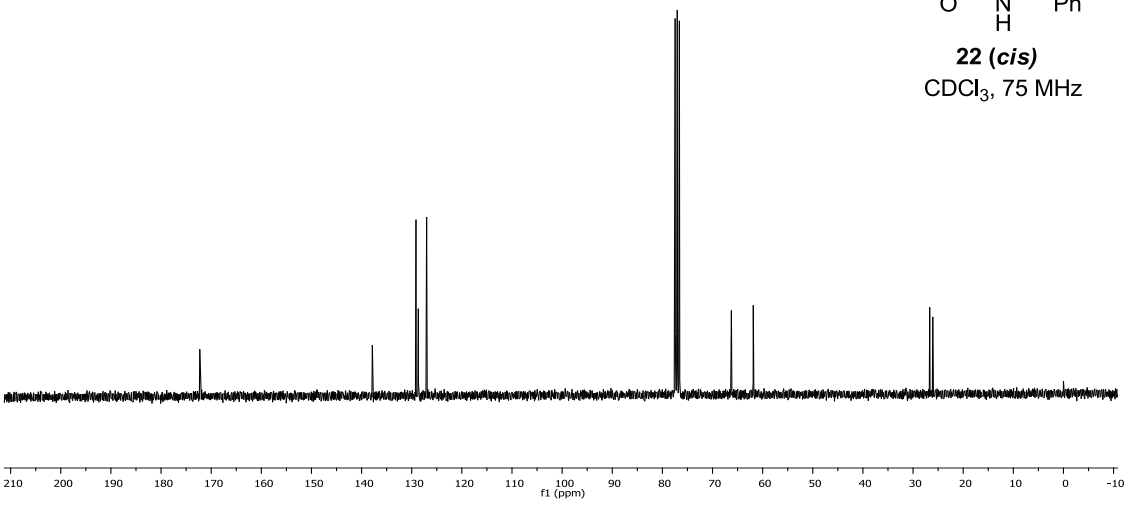

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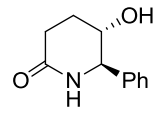

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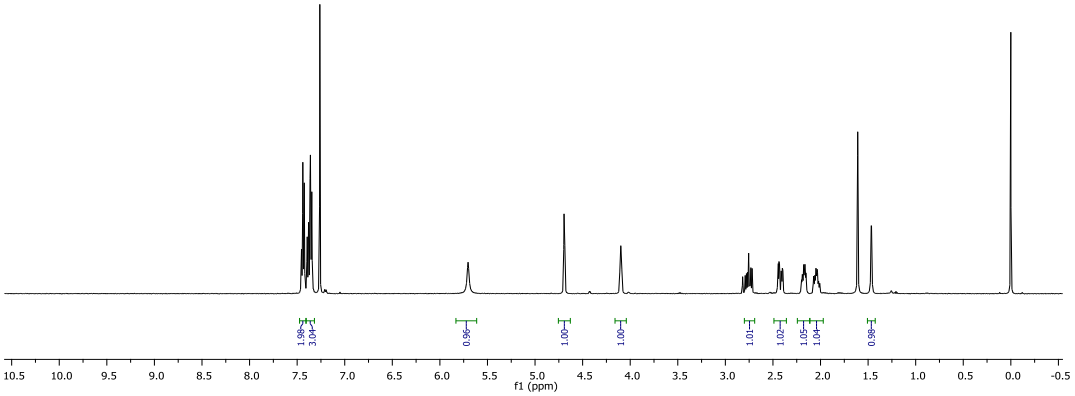

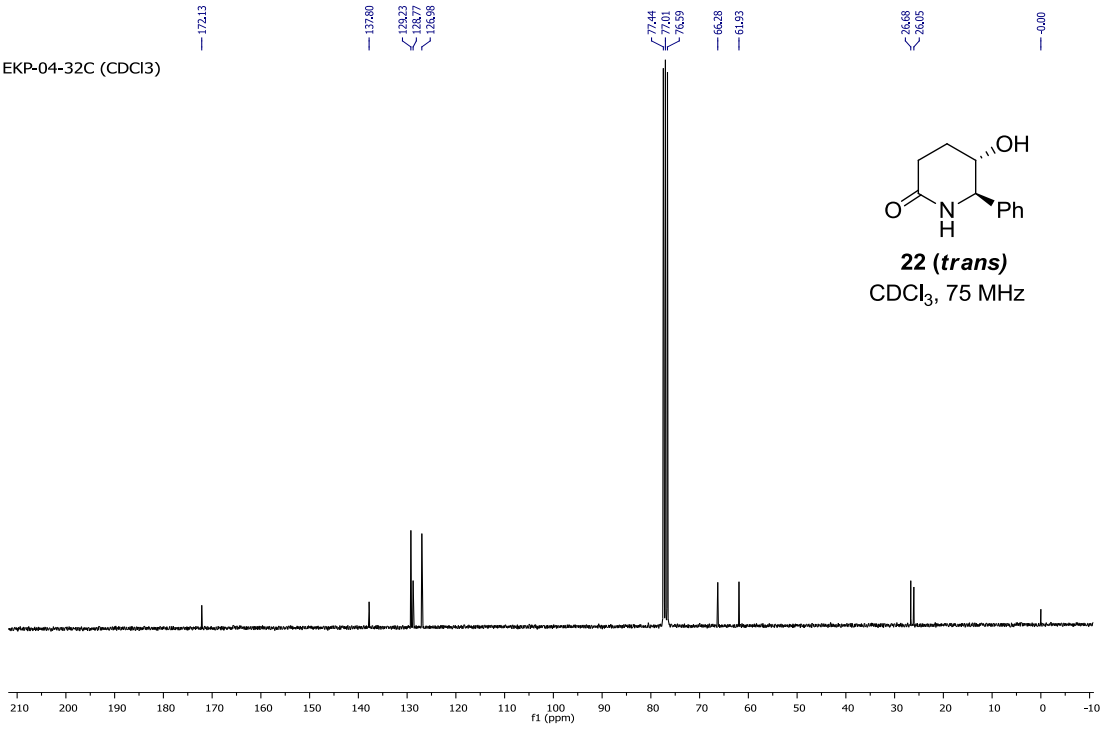

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22 (*trans*)
$CDCl_3$, 75 MHz

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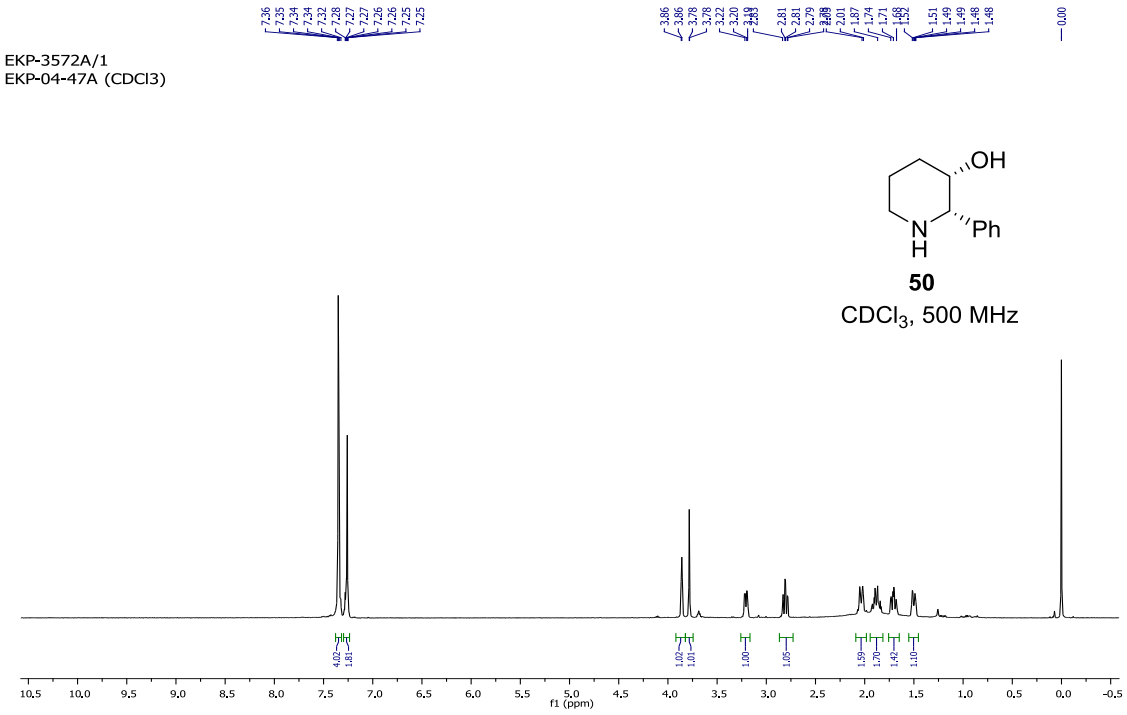
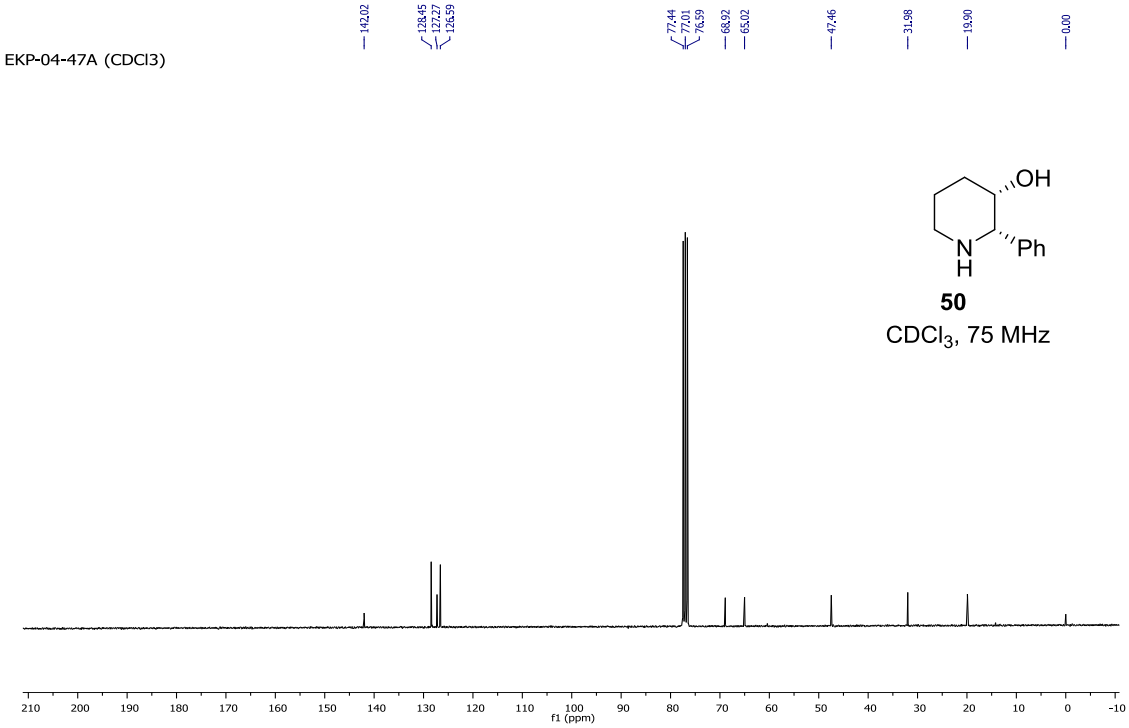


50

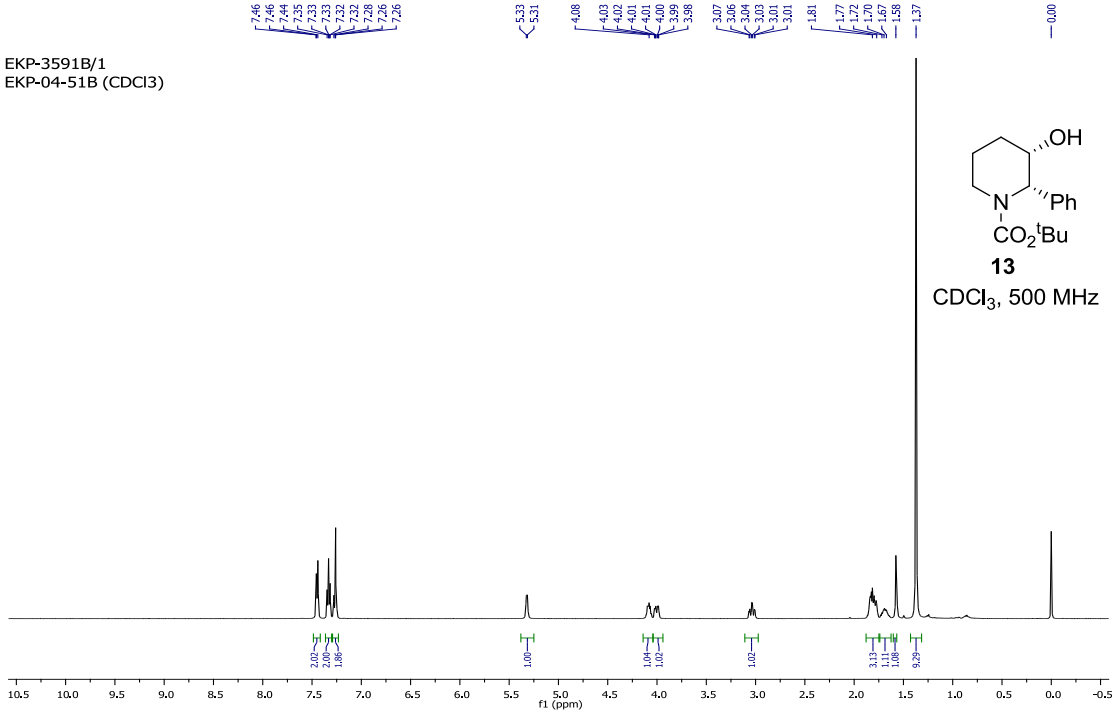
$CDCl_3$, 500 MHz

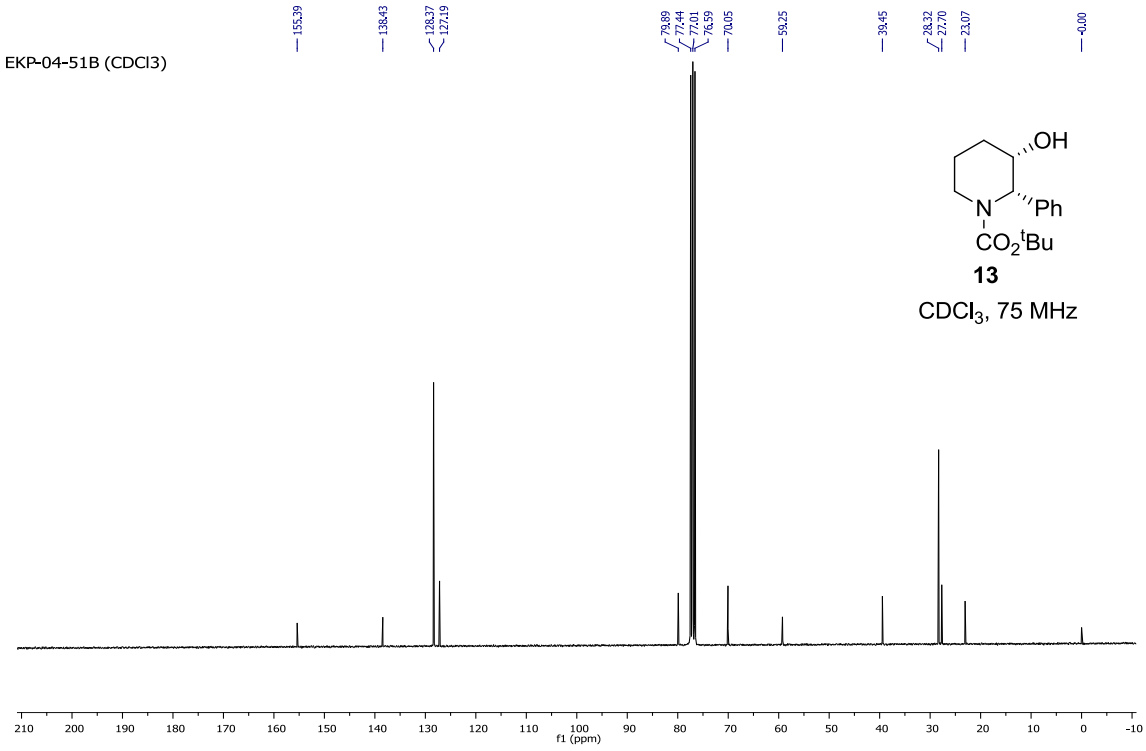
EKP-04-47A (CDCl3)

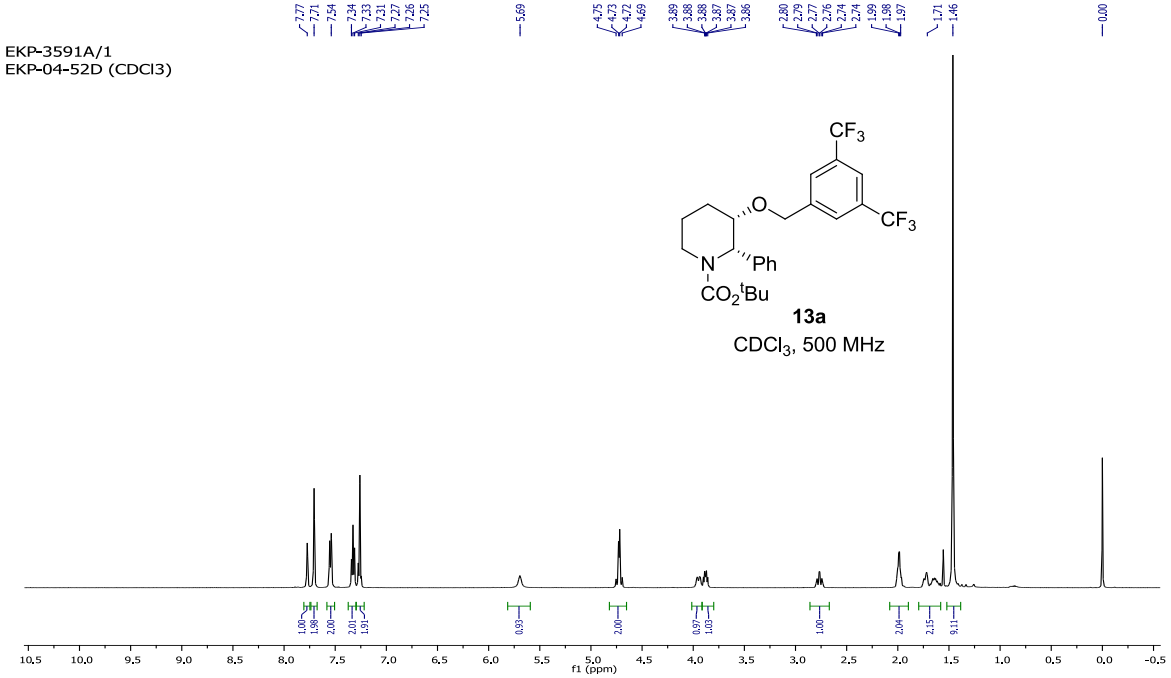


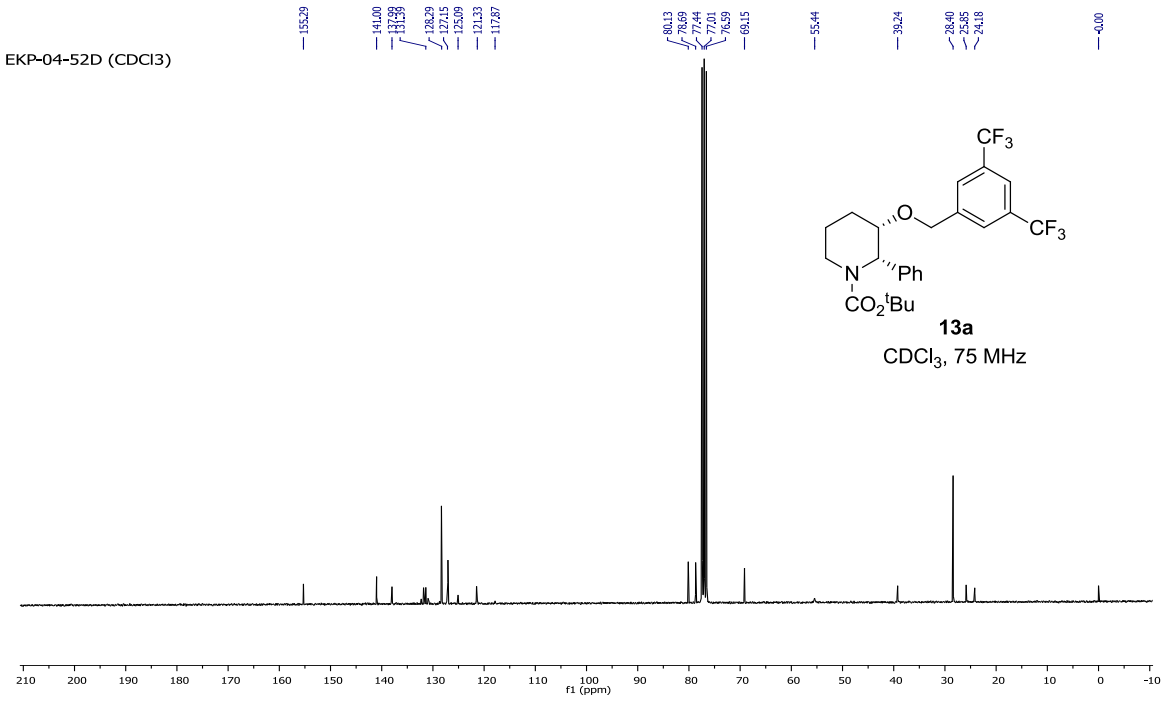
50

$CDCl_3$, 75 MHz

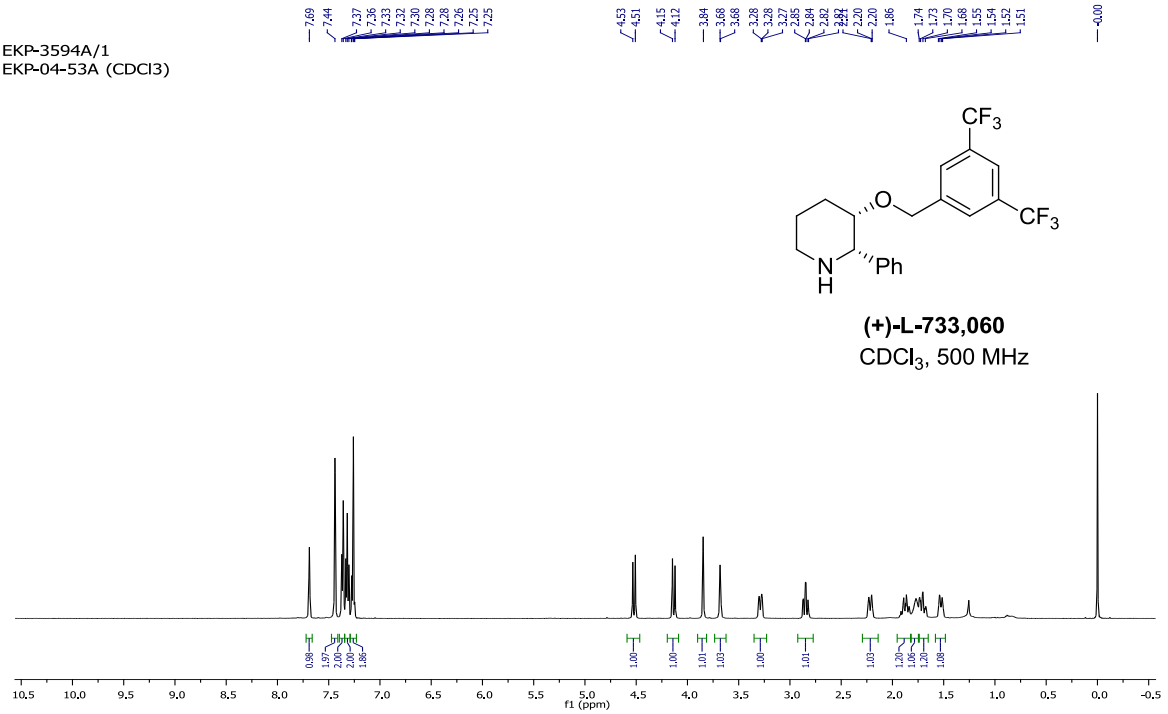

EKP-3591B/1
EKP-04-51B (CDCl3)
OH
Ph
N
CO2tBu
13
CDCl3, 500 MHz
f1 (ppm)


EKP-04-51B (CDCl3)
OH
Ph
N
CO2tBu
13
CDCl3, 75 MHz
f1 (ppm)


EKP-3591A/1
EKP-04-52D (CDCl3)
CF3
CF3
O
N
Ph
CO2tBu
13a
CDCl3, 500 MHz
f1 (ppm)

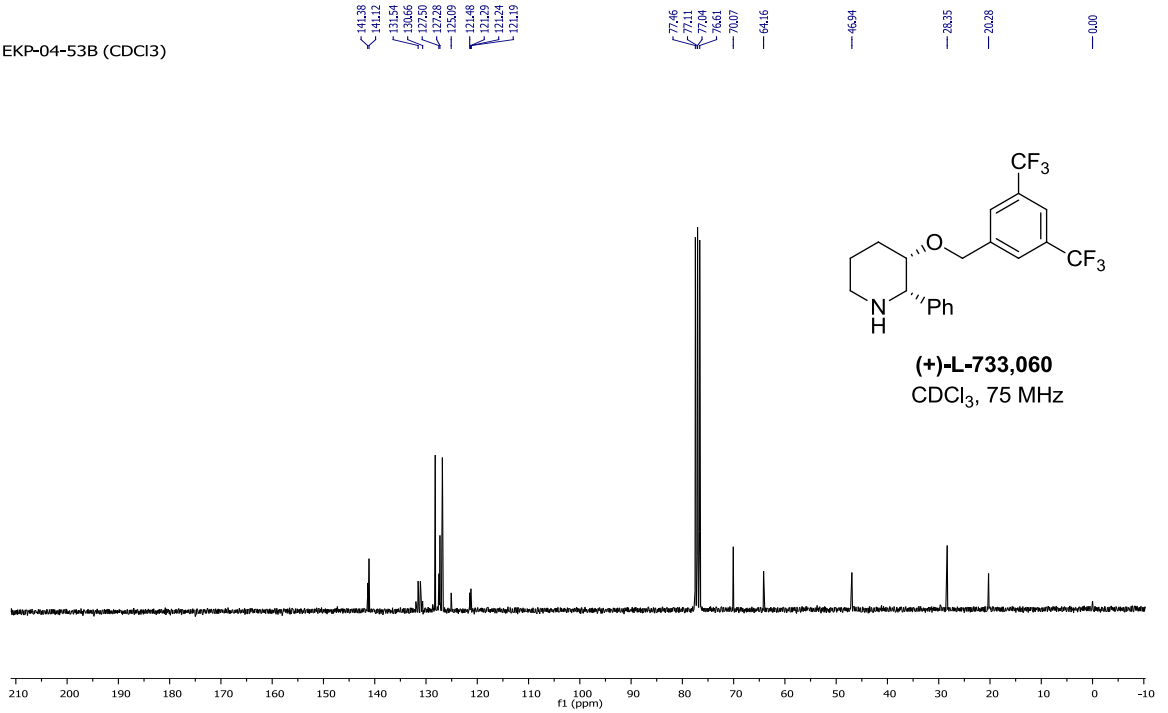

EKP-04-52D (CDCl3)
CF3
CF3
O
N
Ph
CO2tBu
13a
CDCl3, 75 MHz
f1 (ppm)

EKP-3594A/1
EKP-04-53A (CDCl3)

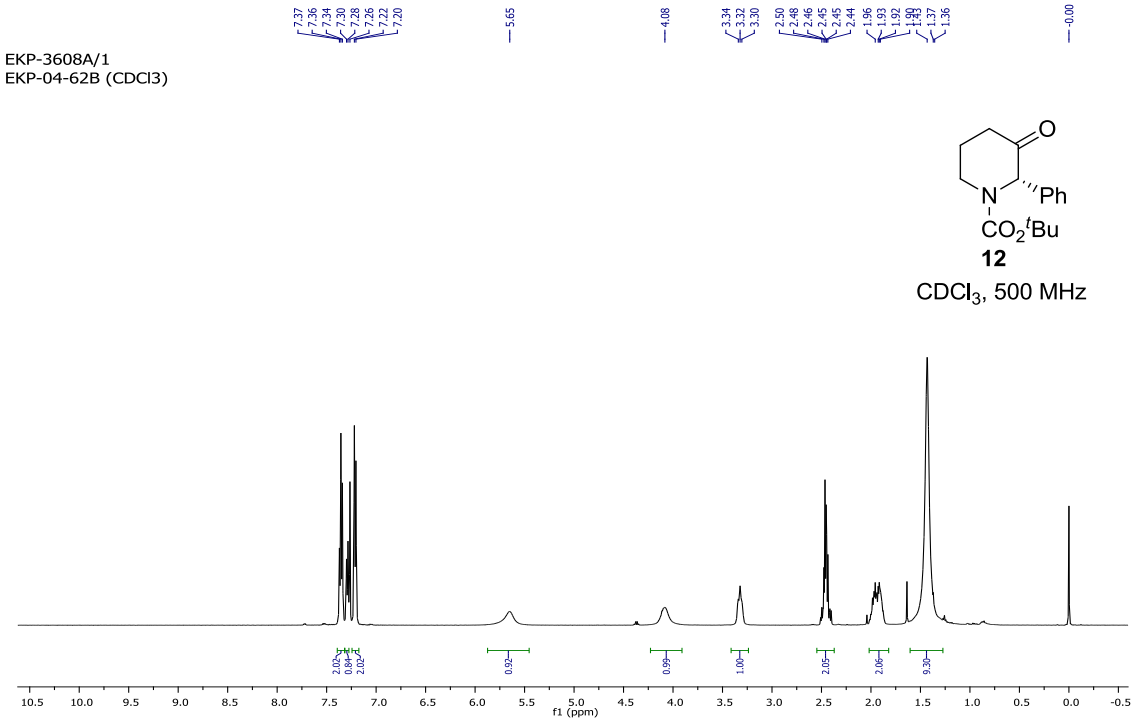


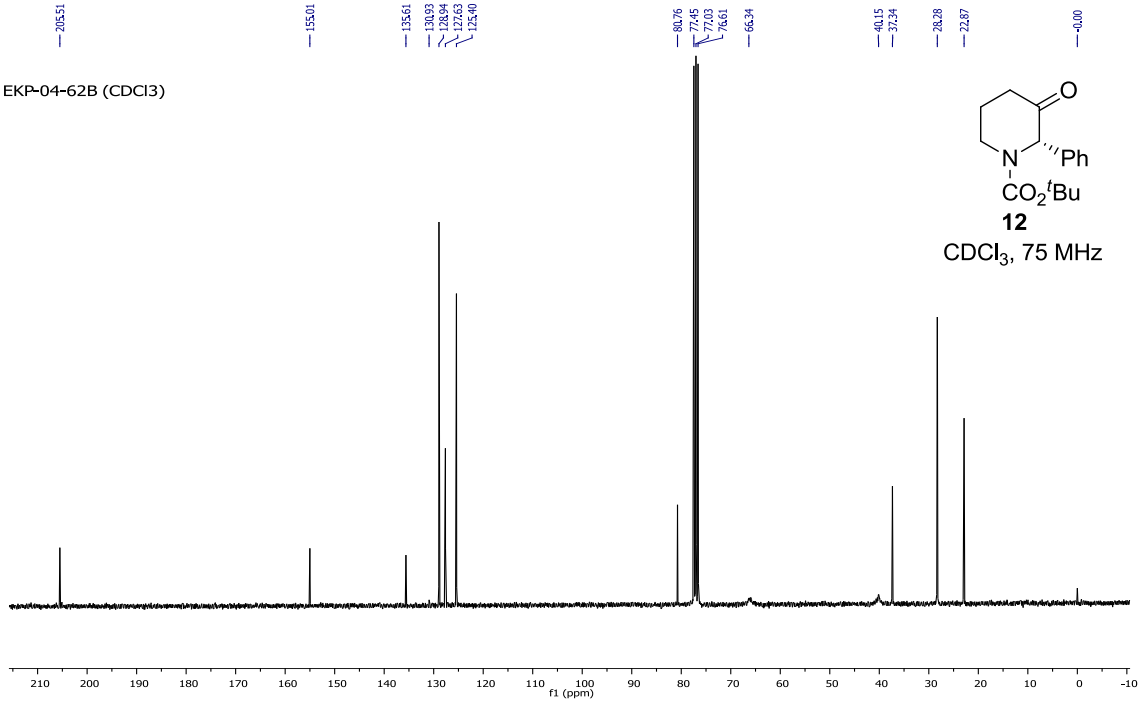
(+)-L-733,060
$CDCl_3$, 500 MHz

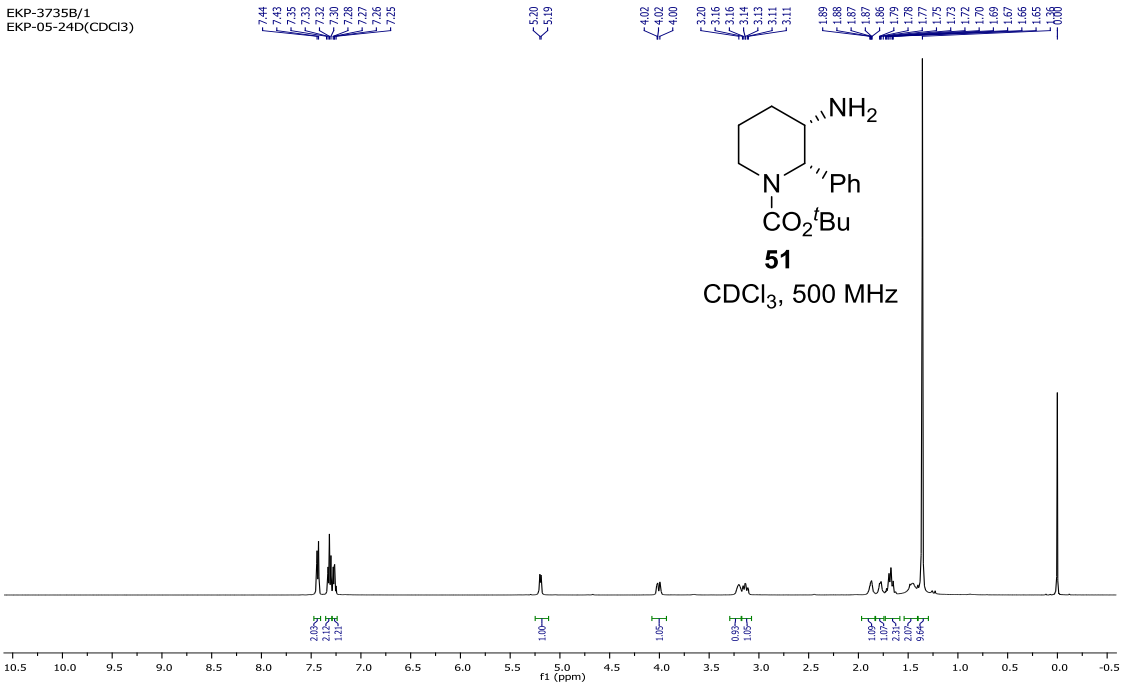
EKP-04-53B (CDCl3)

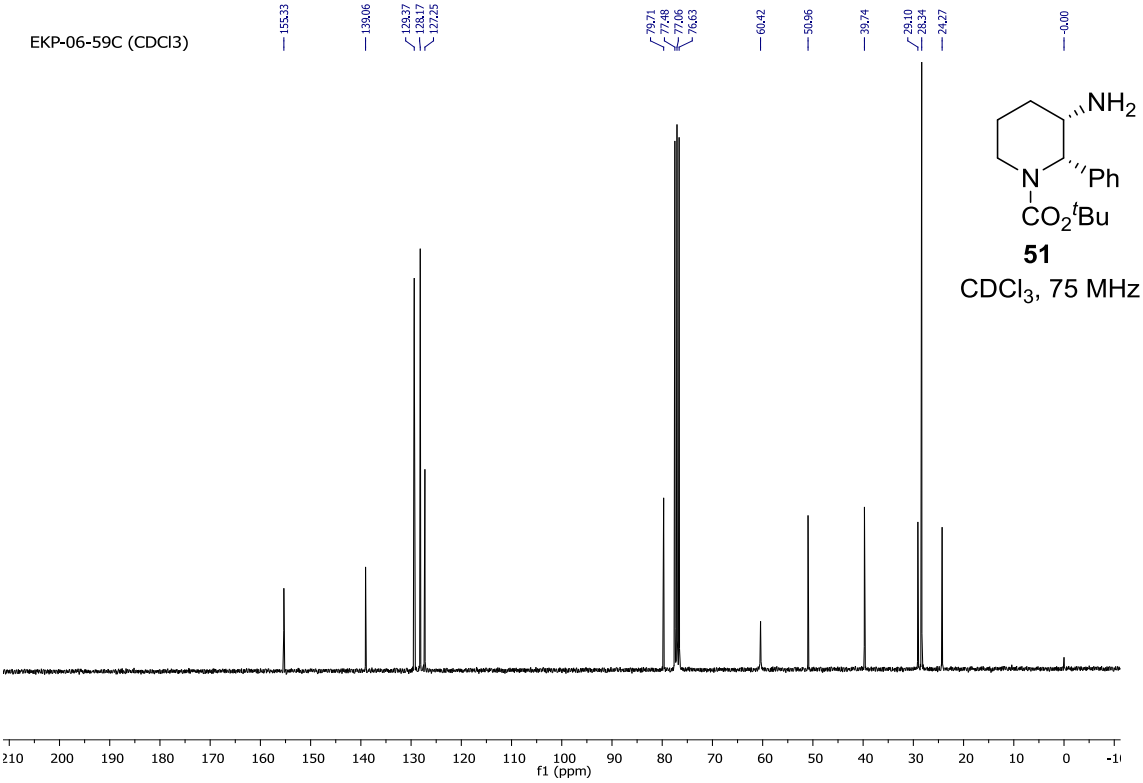


(+)-L-733,060
$CDCl_3$, 75 MHz


EKP-3608A/1
EKP-04-62B (CDCl3)
O
N
Ph
CO2tBu
12
CDCl3, 500 MHz
f1 (ppm)


EKP-04-62B (CDCl3)
O
N
Ph
CO2tBu
12
CDCl3, 75 MHz
f1 (ppm)


EKP-3735B/1
EKP-05-24D(CDCl3)
NH2
Ph
N
CO2tBu
51
CDCl3, 500 MHz
f1 (ppm)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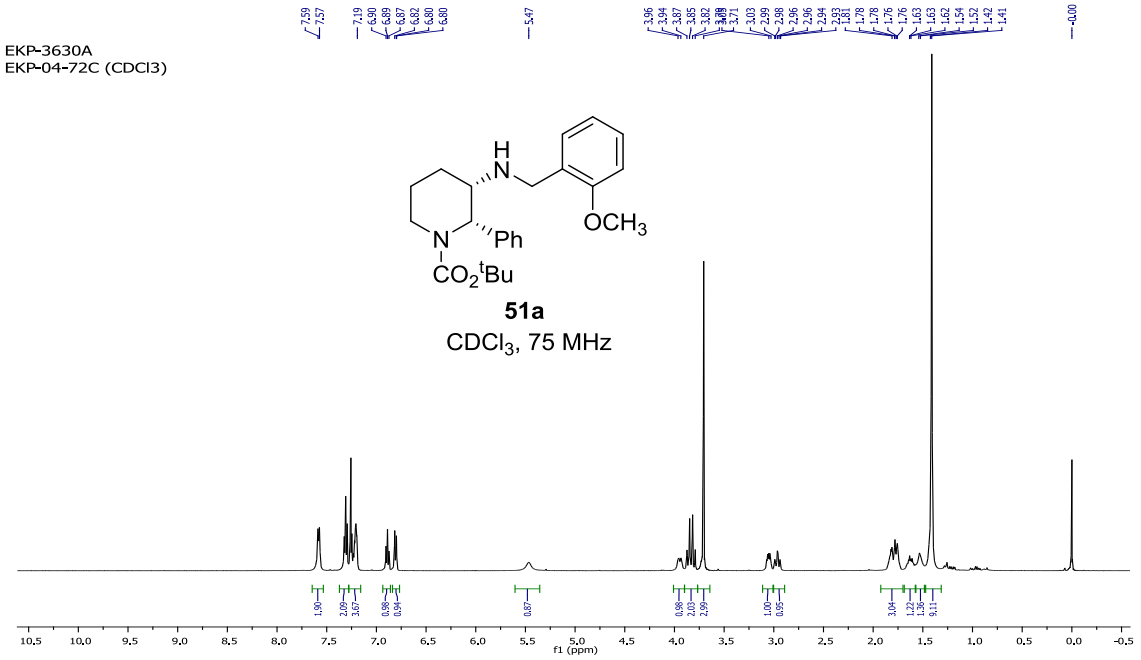
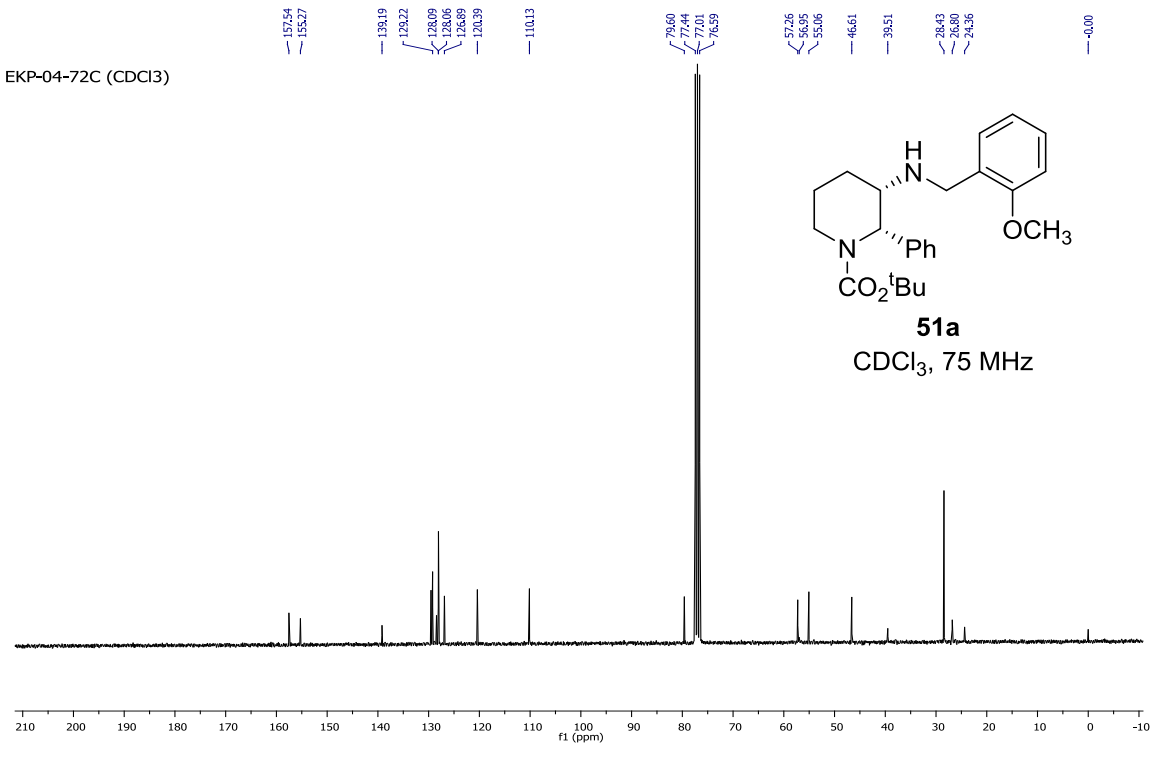
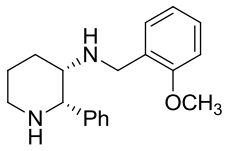
NH2
Ph
N
CO2tBu
51
CDCl3, 75 MHz
f1 (ppm)

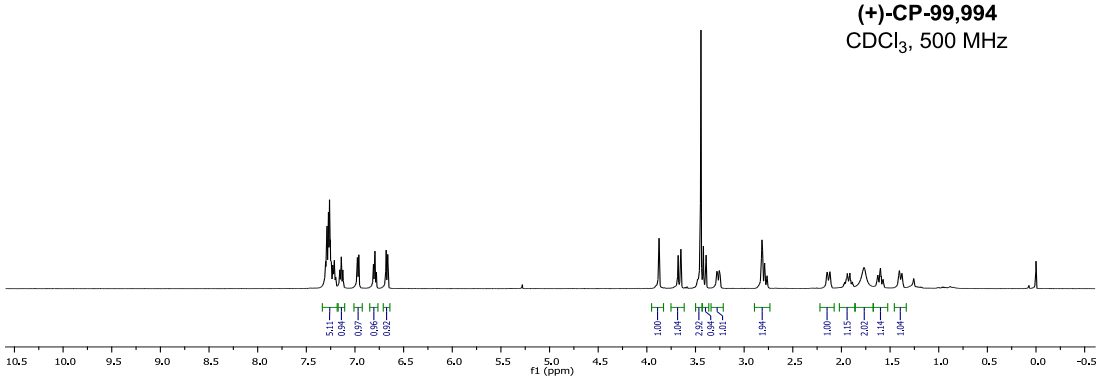

EKP-3630A
EKP-04-72C (CDCl3)
H
N
OCH3
N
Ph
CO2tBu
51a
CDCl3, 75 MHz
f1 (ppm)


EKP-04-72C (CDCl3)
H
N
OCH3
N
Ph
CO2tBu
51a
CDCl3, 75 MHz
f1 (ppm)

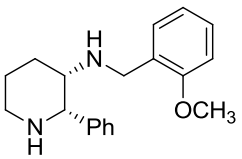
EKP-3634A/1
EKP-04-74A (CDCl3)



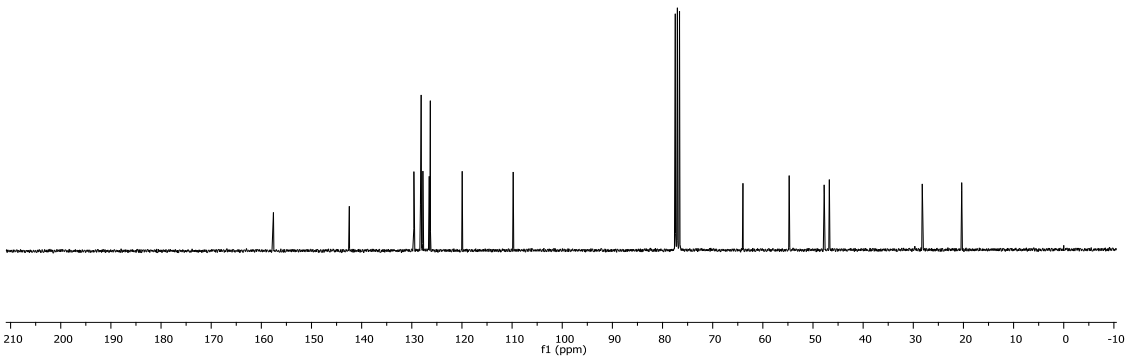
(+)-CP-99,994
$CDCl_3$, 500 MHz

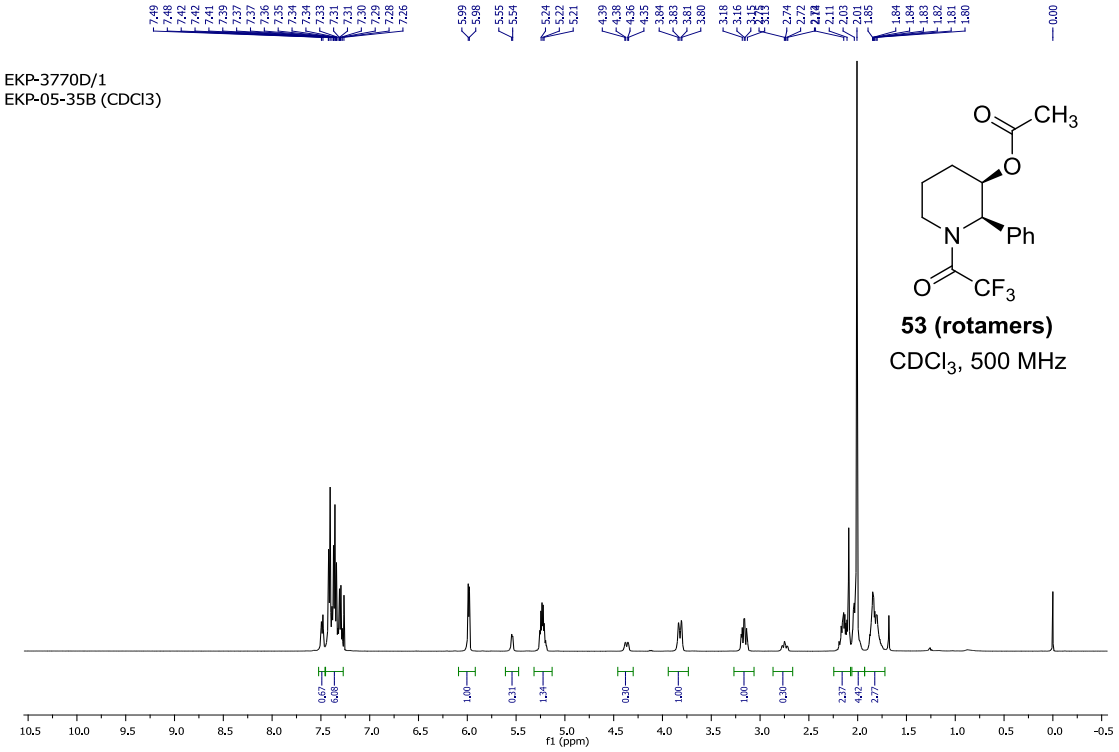


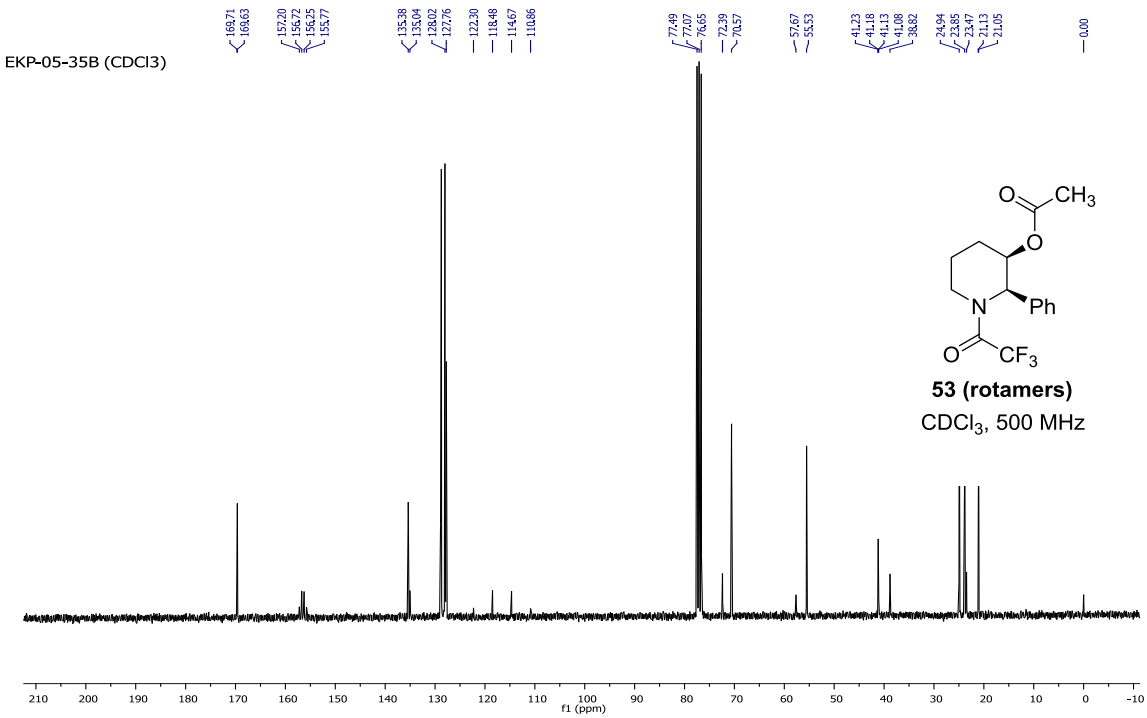
EKP-04-74A (CDCl3)



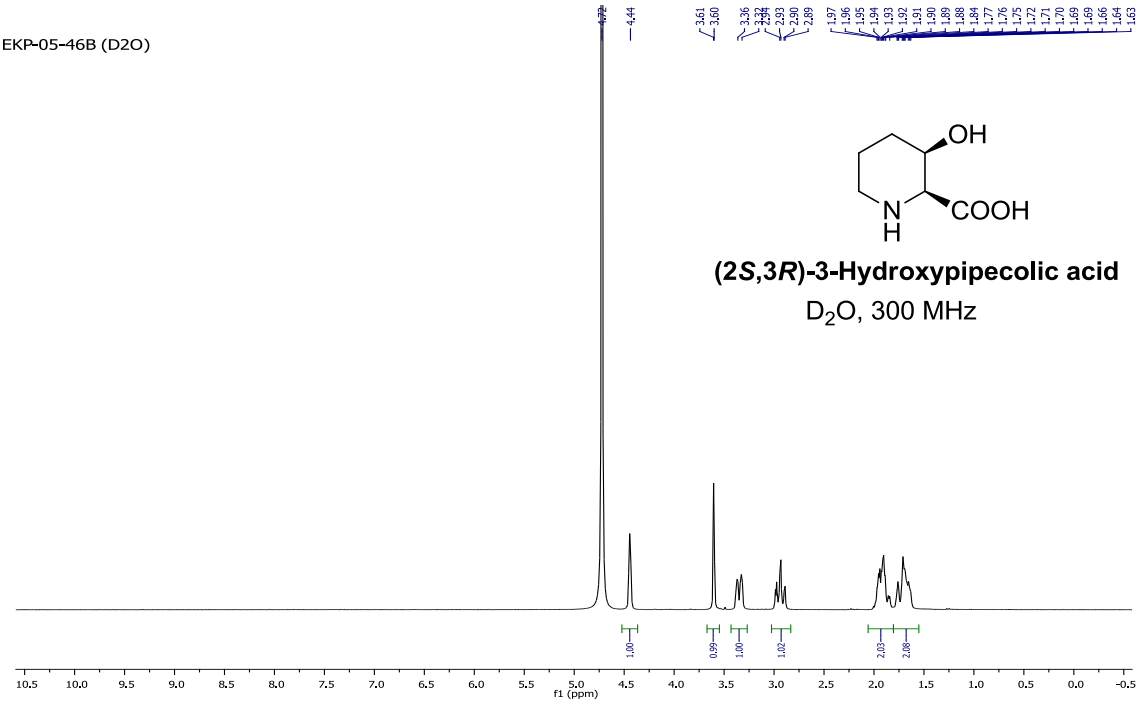
(+)-CP-99,994
$CDCl_3$, 75 MHz




EKP-3770D/1
EKP-05-35B (CDCl3)
53 (rotamers)
CDCl3, 500 MHz
f1 (ppm)


EKP-05-35B (CDCl3)
53 (rotamers)
CDCl3, 500 MHz
f1 (ppm)

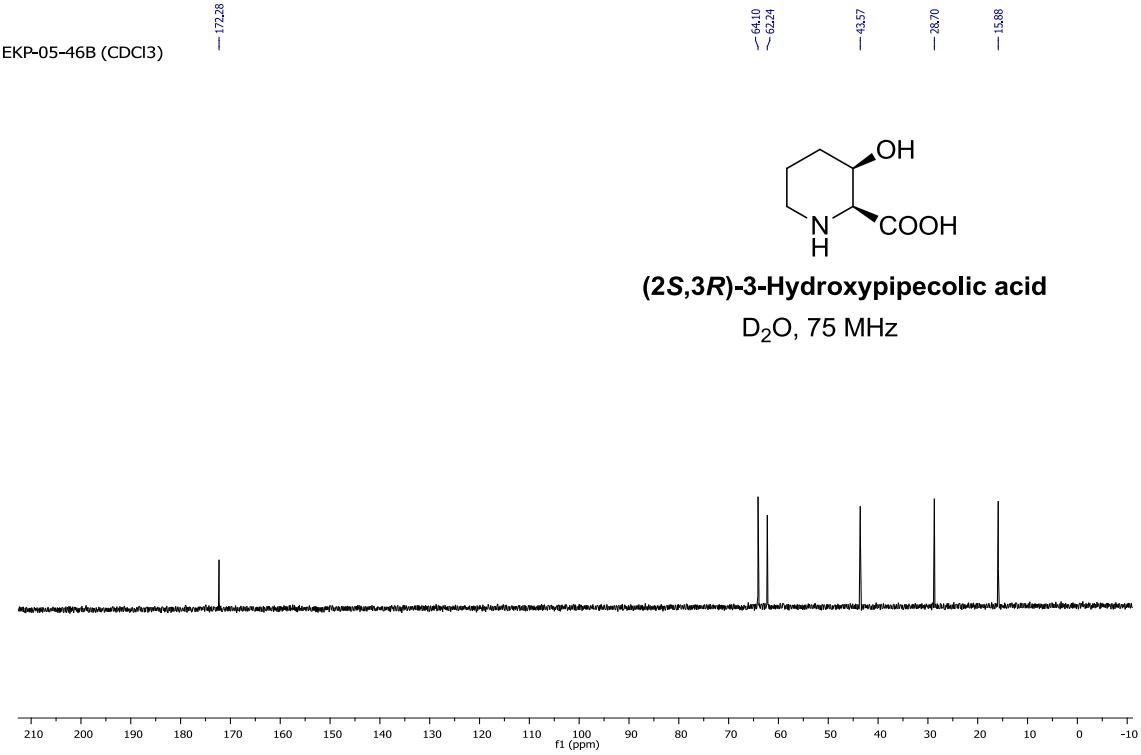
EKP-05-46B (D2O)



(2*S*,3*R*)-3-Hydroxypipecolic acid

D_2O, 300 MHz

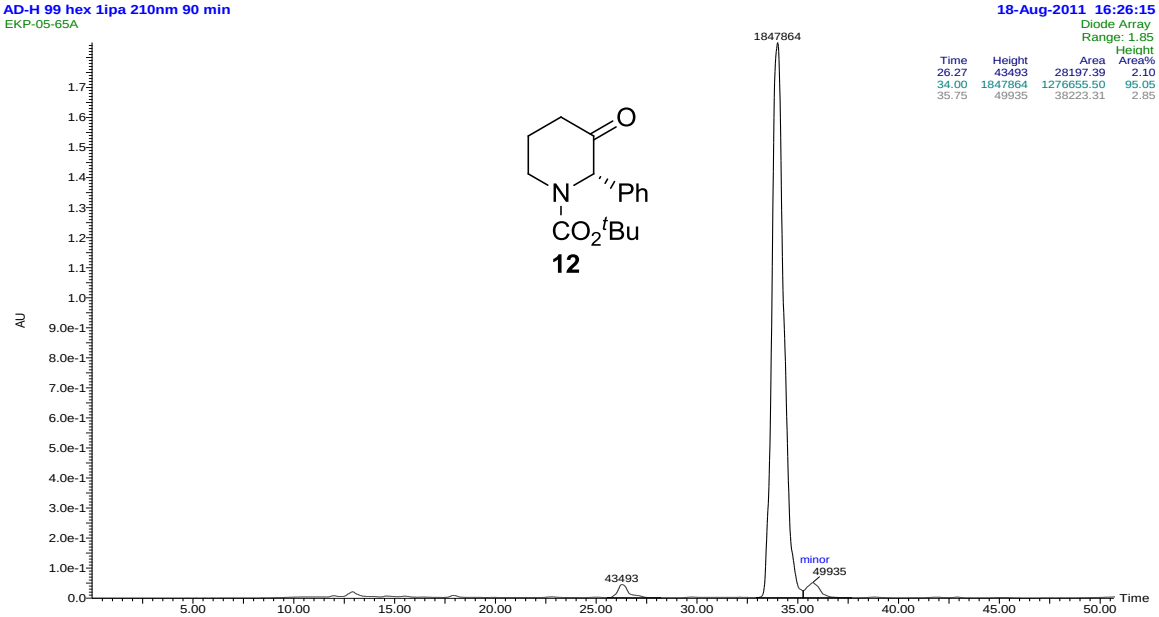
EKP-05-46B (CDCl3)

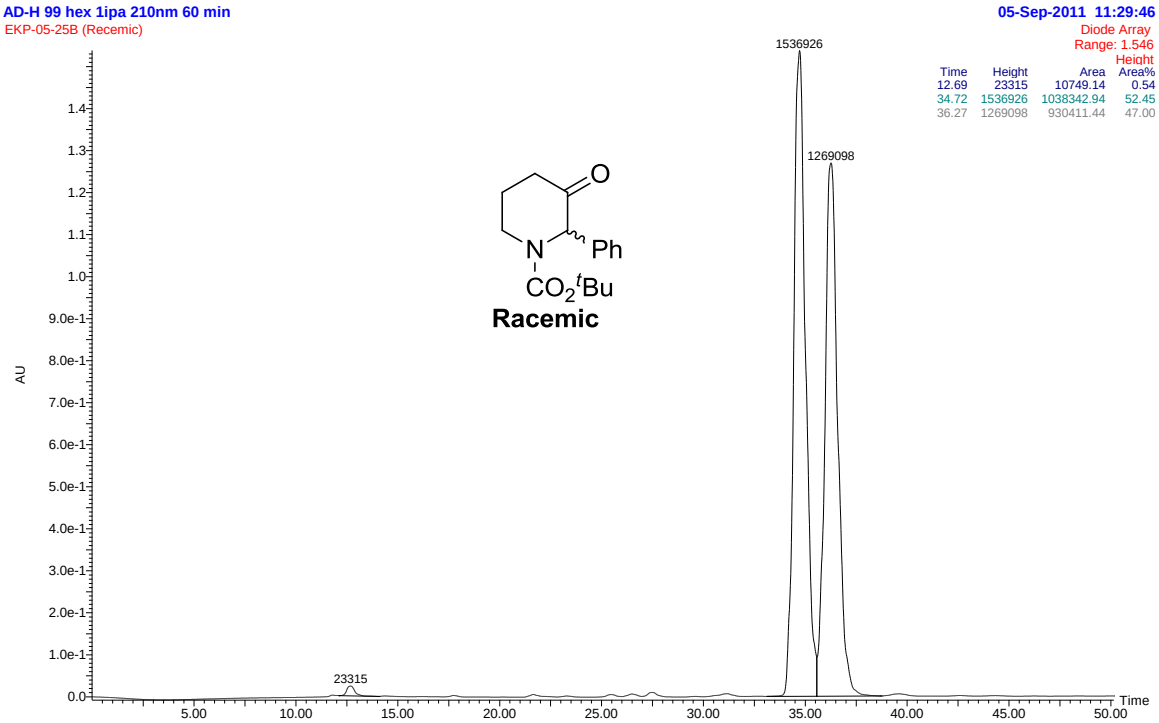


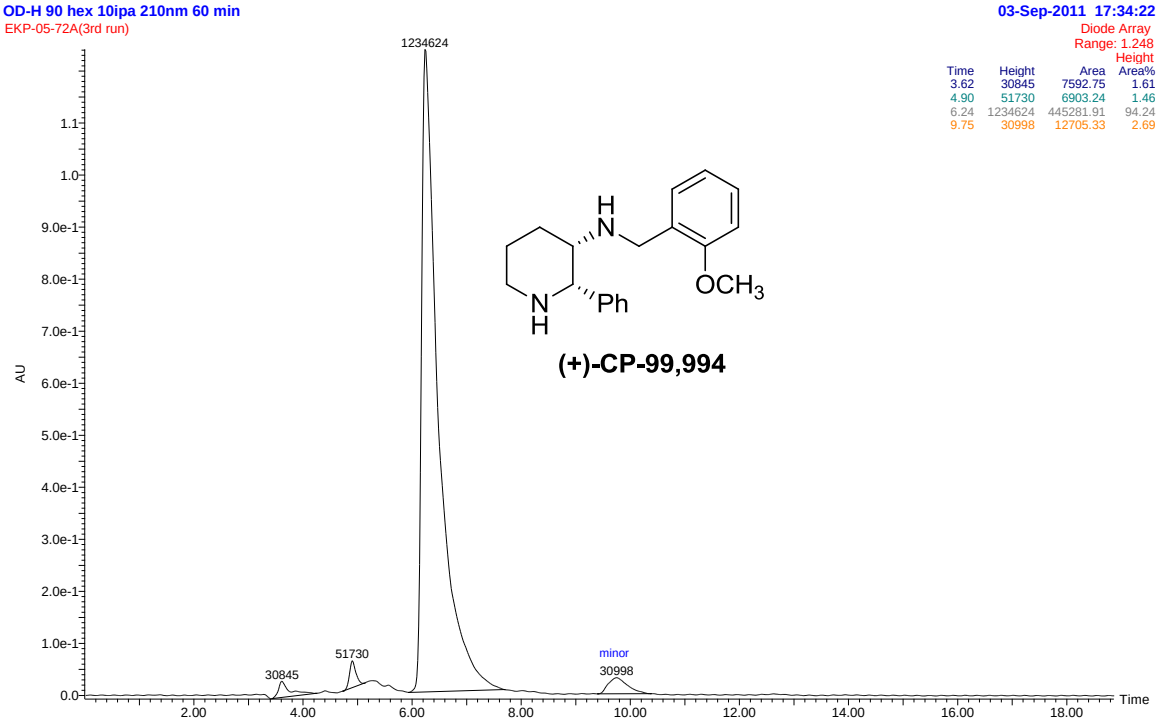
(2*S*,3*R*)-3-Hydroxypipecolic acid

D_2O, 75 MHz

3.8 Selected HPLC chromatograms


AD-H 99 hex 1ipa 210nm 90 min
EKP-05-65A
18-Aug-2011 16:26:15
Diode Array
Range: 1.85
Height
Time Height Area Area%
26.27 43493 28197.39 2.10
34.00 1847864 1276655.50 95.05
35.75 49935 38223.31 2.85
1847864
O
N
Ph
CO2tBu
12
minor
49935
43493
AU
Time


AD-H 99 hex 1ipa 210nm 60 min
EKP-05-25B (Recemic)
05-Sep-2011 11:29:46
Diode Array
Range: 1.546
Height
Time Height Area Area%
12.69 23315 10749.14 0.54
34.72 1536926 1038342.94 52.45
36.27 1269098 930411.44 47.00
1536926
1269098
O
N
Ph
CO2tBu
Racemic
23315
AU
Time


OD-H 90 hex 10ipa 210nm 60 min
EKP-05-72A(3rd run)
03-Sep-2011 17:34:22
Diode Array
Range: 1.248
Height
Time Height Area Area%
3.62 30845 7592.75 1.61
4.90 51730 6903.24 1.46
6.24 1234624 445281.91 94.24
9.75 30998 12705.33 2.69
1234624
30845
51730
minor
30998
AU
Time
(+)-CP-99,994

CHAPTER 4

Synthesis of (+)-Febrifugine and a Formal Synthesis of (+)-Halofuginone Employing an Organocatalytic Direct Vinylogous Aldol Reaction

This Chapter is based on the following publication:

Pansare, S. V.; Paul, E. K. *Synthesis* **2013,** *45*, 1863-1869.

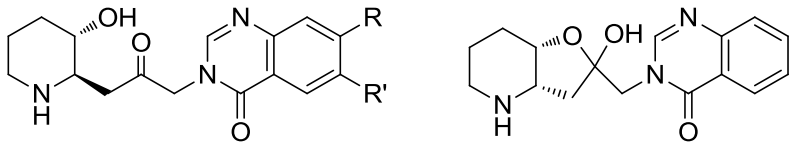
Contributions of authors

S. V. Pansare: research supervisor, manuscript preparation.

E. K. Paul: experimental work, manuscript preparation.

4.1 Introduction

The prevalence of malaria in tropical regions and the need for new medicines to combat malaria have resulted in a persistent, and often challenging, search for new antimalarial agents.[1] In this context, febrifugine (**1**, Figure 4.1) and halofuginone (**2**) have attracted considerable interest due to their pronounced antimalarial activity.[2] In solution, febrifugine (**1)** is gradually converted to isofebrifugine (**3**) which is less potent, but exhibits antimalarial activity similar to febrifugine.[2d] The asymmetric synthesis of febrifugine[3] continues to be actively investigated and the reported syntheses often showcase new methodology for stereoselective construction of the 2,3-disubstituted piperidine ring in the targets. Only two asymmetric syntheses of halofuginone[3a,4] are reported. Febrifugine and halofuginone also have numerous other applications which have contributed to a continued interest in these alkaloids. Notably, in addition to its antimalarial properties, halofuginone is used as an antiprotozoal agent in poultry[5] and it is also an antiangiogenic agent.[6] It has been approved for the treatment of scleroderma and it is active against oestrogen-deficient osteoporosis in mice.[7] Recently, the molecular mechanism of action of febrifugine and halofuginone in mice has been determined.[8] These studies highlighted the importance of structural analogs of febrifugine in the treatment of multiple sclerosis, scleroderma and rheumatoid arthritis. Hence, an important consideration in devising a synthesis of the title compounds is the flexibility of the approach for making analogs of febrifugine.



1: R = R' =H **2**: R = Br, R' = Cl **3**

Figure 4.1. (+)-Febrifugine (**1**), (+)-halofuginone (**2**) and isofebrifugine (**3**).

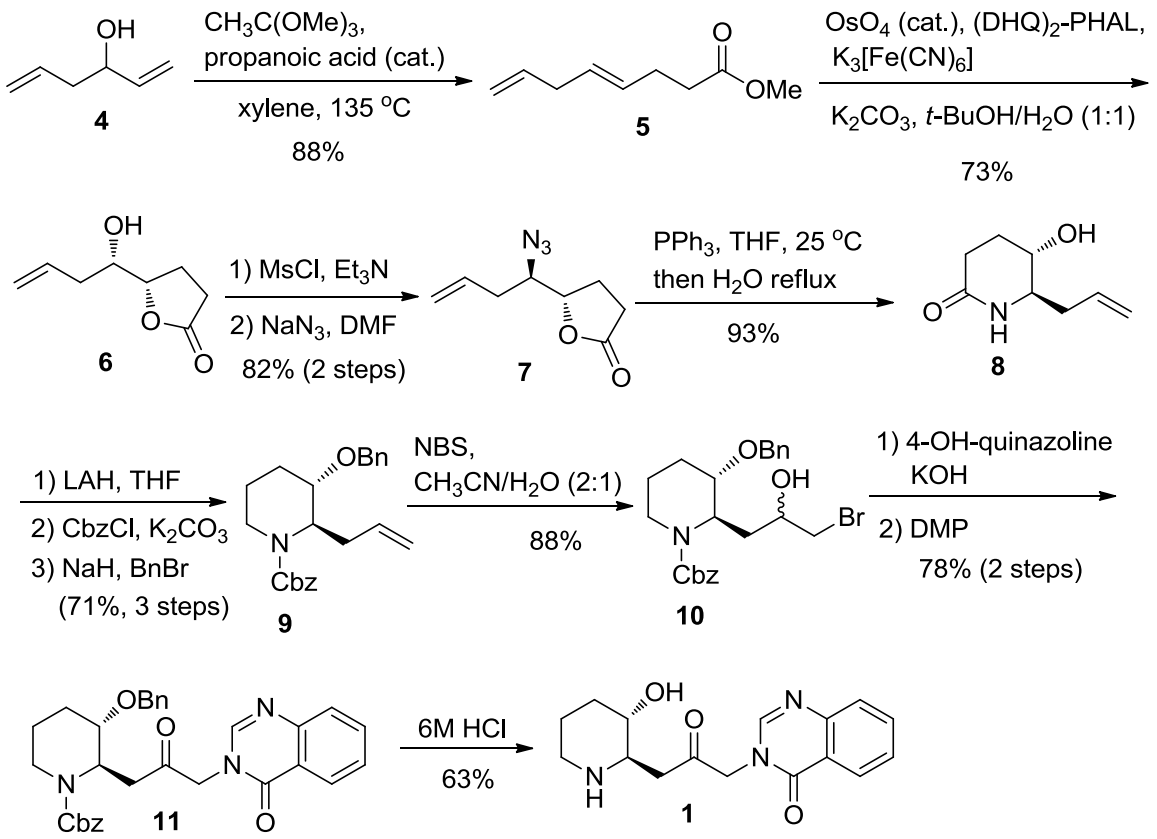
4.2 Known synthetic routes to (+)-Febrifugine

The following summary provides an overview of selected reported syntheses of (+)-febrifugine from 2009 onwards.

4.2.1 The Sudalai synthesis of (+)-Febrifugine

Sudalai and coworkers reported[3f] an enantioselective synthesis of (+)-febrifugine. The synthesis started from the commercially available 1,5-hexadien-3-ol **4**, which undergoes Claisen-Johnson rearrangement to afford the ester **5** (Scheme 4.1). The Os-catalyzed regioselective ADH of 1,4-dienic ester **5** using $(DHQ)_2$-PHAL as the chiral ligand provided hydroxyl lactone **6**. The secondary alcohol in **6** was protected as its mesylate followed by displacement of the mesylate, with inversion of configuration, by azide anion gave the azido butyrolactone **7**. Under Staudinger conditions, the azide **7** undergoes reductive cyclization to the piperidinone **8**. Reduction of the lactam in **8** using $LiAlH_4$ provided the corresponding piperidine, which was treated with benzyl chloroformate. Subsequent benzylation of the secondary alcohol using benzyl bromide afforded the key intermediate **9**. The regioselective bromohydroxylation of **9** using NBS provided the terminal halide **10** as a diastereomeric mixture (dr = 1.5:1). This was treated

with 4-hydroxyquinazoline in the presence of KOH followed by the oxidation of secondary alcohol to ketone using Dess-Martin periodinane to provide protected febrifugine **11**. Deprotection of **11** (6 M HCl) and subsequent neutralization provided (+)-febrifugine (12 steps from **4**, 15% overall yield).

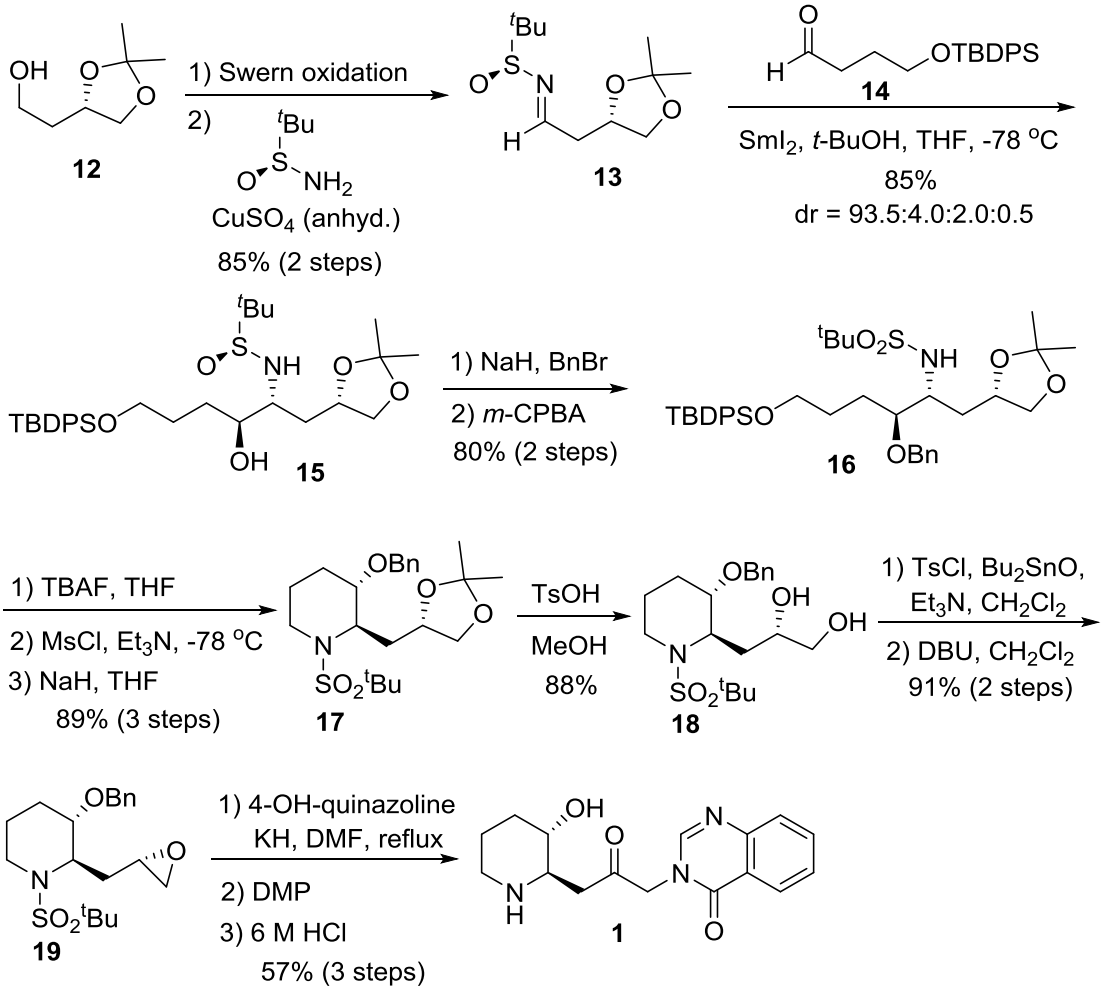


Scheme 4.1. Synthesis of (+)-febrifugine by Sudalai.

4.2.2 The Lin synthesis of (+)-Febrifugine

In 2009, Lin and coworkers reported[3b] an asymmetric total synthesis of (+)-febrifugine. The synthesis began with the Swern oxidation of **12** to afford the aldehyde,

which was treated with *tert*-butanesulfinamide to provide the imine **13** (Scheme 4.2). The SmI_2-mediated reductive cross-coupling reaction of imine **13** with the aldehyde **14** under -78 ^{o}C afforded the amido alcohol **15** in good yield and diastereoselectivity (93.5:4.0:2.0:0.5). Protection of the hydroxyl group in **15** as the benzyl ether and subsequent treatment with *m*-CPBA gave the sulfonamide **16**. After removal of the silyl group in **16** with TBAF, mesylation of the hydroxyl group followed by base-induced cyclization provided the *N*-sulfonyl piperidine **17**. Treatment of **17** with *p*-toluenesulfonic acid in methanol to afforded the diol **18**. Monotosylation of **18** followed by base mediated cyclization provided the epoxide **19**. Opening the epoxide with the anion of 4-hydroxyquinazoline followed by the oxidation of the secondary alcohol using Dess-Martin periodinane gave protected febrifugine. This was deprotected using 6 M HCl to provide (+)-febrifugine (14 steps from **12**, 23.5% overall yield).

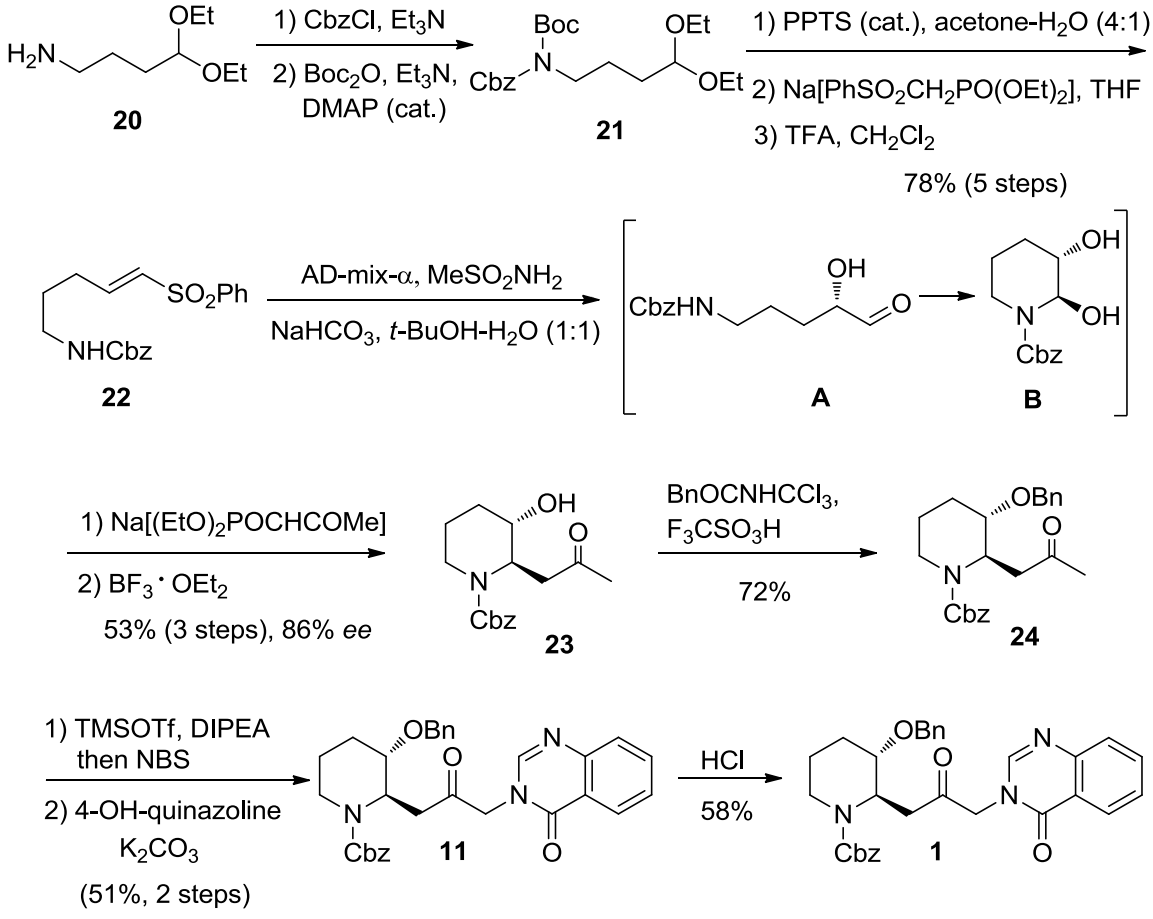


Scheme 4.2. Synthesis of (+)-febrifugine by Lin.

4.2.3 The Evans synthesis of (+)-Febrifugine

Evans and coworkers reported[3a] an enantioselective synthesis of (+)-febrifugine. The synthesis started from 4-aminobutyraldehyde diethylacetal **20**, which was protected with benzyl chloroformate followed by di-*tert*-butyl dicarbonate to afford **21** (Scheme 4.3). The acetal in **21** was removed with pyridinium *p*-toluenesulfonate to provide the aldehyde. Treatment of the aldehyde with (benzenesulfonylmethyl)phosphonic acid

diethyl ester in presence of NaH followed by deprotection provided the vinyl sulfone **22**. Treatment of **22** with AD-mix-α afforded the hemiaminal **B**, Horner-Wadsworth-Emmons olefination of the hemiaminal followed by treatment with $BF_3 \cdot OEt_2$ gave the piperidine **23**. The hydroxyl group in **23** was protected as the benzyl ether to afford piperidine **24**. Bromination of the ketone in **24** (TMSOTf, DIPEA then NBS) followed by treatment of the crude bromoketone with 4-hydroxyquinazoline provided the protected febrifugine derivative **11**. Deprotection of **11** (HCl) and subsequent neutralization provided (+)-febrifugine (12 steps from **20**, 8.8% overall yield).



Scheme 4.3. Synthesis of (+)-febrifugine by Evans.

4.3 Results and Discussion

We decided to develop a synthesis of febrifugine that would proceed through a precursor that could also be converted into halofuginone and, potentially, other heteroaryl linked piperidines by simple coupling with a suitable heterocycle. Retrosynthetically, the common precursor to **1** or **2** is a suitably protected piperidinyl bromoketone[3j] such as **C** (Figure 4.2) which derives from the functionalized piperidinone **D**. The piperidinone **D** can be obtained by isomerization[9] of an amino alkyl lactone such as **E**. Ultimately, **E** derives from the functionalized butenolide **F** which leads to the organocatalytic direct vinylogous aldol reaction[10] of crotonolactone and an appropriate aldehyde. The vinylogous aldol reaction[11] directly sets the absolute stereochemistry at C-5 in the piperidine ring of the target. The stereochemistry at C-6 is indirectly controlled by the aldol reaction and is achieved by manipulation of the secondary alcohol stereocenter in the aldol adduct (Figure 4.2).

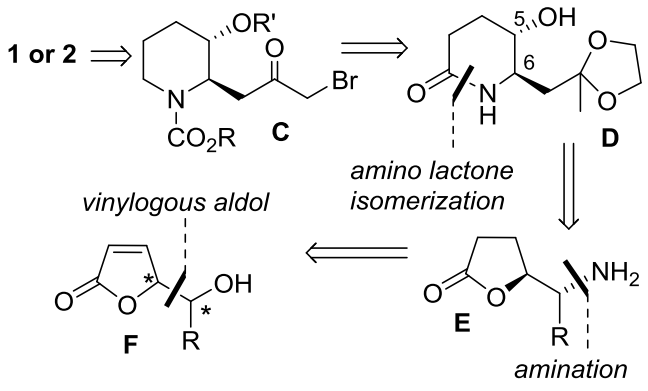


Figure 4.2. The organocatalytic direct vinylogous aldol route to febrifugine.

Our investigations began with the synthesis of **28** (Scheme 4.4). Initially, the direct vinylogous aldol reaction of commercially available γ-crotonolactone **26** and the aldehyde **27**[12] was examined in the presence of selected cyclohexanediamine, diphenylethylenediamine and cinchonidine derived thioureas[13] (**25a**, **25b**, **25c**) and cyclohexanediamine and diphenylethylenediamine derived squaramides[14] (**25d** and **25e**, Figure 4.3).

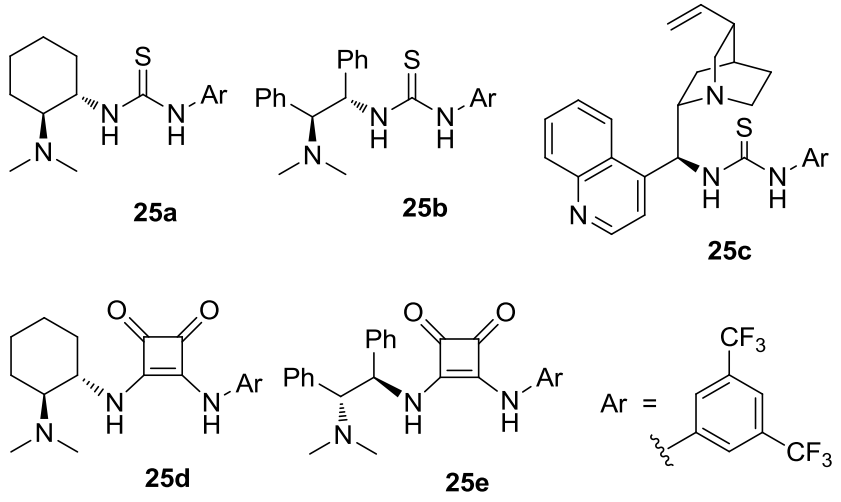
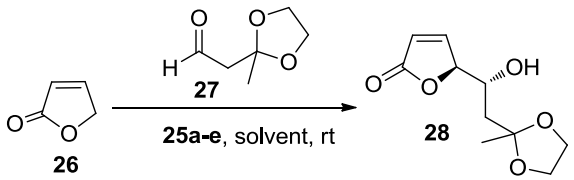


Figure 4.3. Selected aminothiourea and aminosquaramide catalysts.

Orienting experiments with the catalyst **25a** suggested dichloromethane as a solvent for further studies based on the yield and enantiomeric excess of **28** (Table 4.1, entries 1-4). Although lowering the temperature (0 ^{o}C) increased the diastereoselectivity and enantiomeric excess for **28**, the reaction was prohibitively slow (Table 4.1, entry 5, 8% yield of **28**). The diphenylethylenediamine-derived aminothiourea **25b** was ineffective as a catalyst and provided only a trace of **28** in dichloromethane (Table 4.1, entries 6-8). Catalyst **25c** provided **28** in low yield and moderate enantiomeric excess

(Table 4.1, entry 9). Reactions with the aminosquaramide catalysts **25d** and **25e** were slower, but provided **28** with higher enantiomeric excess (Table 4.1, entries 10-16) than the aminothiourea catalysts **25a-c**. For catalyst **25d**, the use of dichloromethane as the solvent provided the highest enantiomeric excess (Table 4.1, entries 10-12) but the yield and diastereostelectivity for **28** remained low. Further studies with the aminosquaramide catalyst **25e**[14a] in ethyl acetate provided **28** with good enantiomeric excess (95%) but low diastereoselectivity and yield. In comparison, the reaction with **25e** was synthetically more useful when dichloromethane was used as the solvent (Table 4.1, entries 14-16).

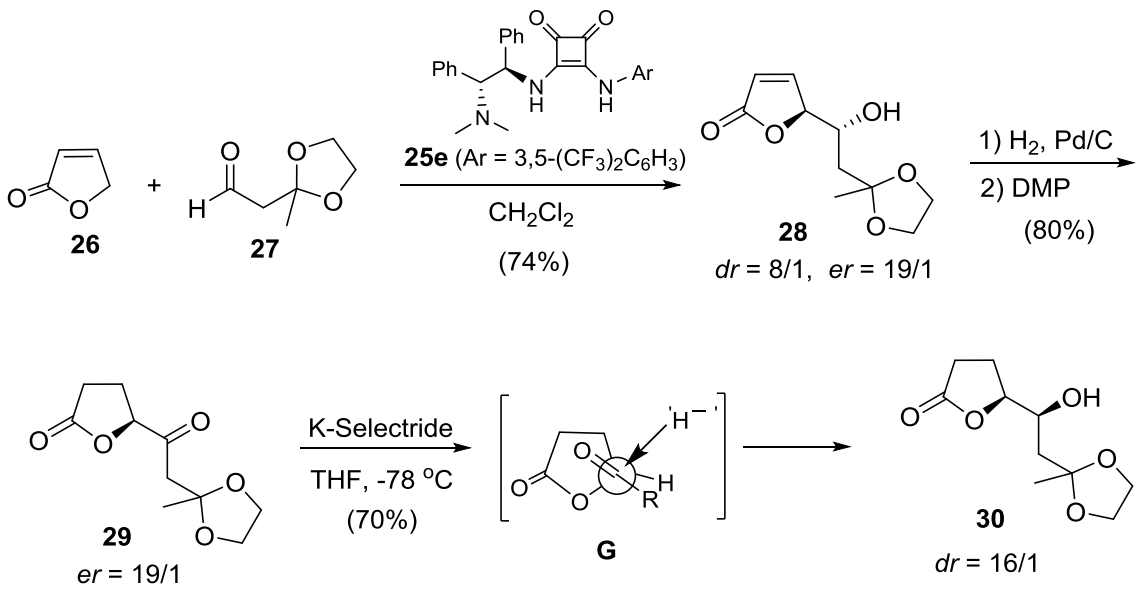


Entry[a]	Cat[b]	Solvent	T/h	Yield (%)	dr[c] (*anti/syn*)	ee[d] (%) (*anti*)[e]
1	**25a**	CH_2Cl_2	24	59	1.1/1	−55
2	**25a**	toluene	24	68	1/1	−18
3	**25a**	EtOAc	24	31	1.1/1	−58
4	**25a**	DMF	24	12	1/1	−30
5	**25a**	CH_2Cl_2	144[f]	8	4.2/1	−62
6	**25b**	CH_2Cl_2	144	2	-	−61
7	**25b**	EtOAc	144	0	-	-
8	**25b**	toluene	144	0	-	-
9	**25c**	CH_2Cl_2	48	13	1.5/1	−74
10	**25d**	CH_2Cl_2	48	31	1.9/1	−90
11	**25d**	CH_2Cl_2	144[f]	16	2.2/1	−93
12	**25d**	EtOAc	48	20	1.6/1	−88
13	**25d**	toluene	48	39	1.5/1	−88
14	**25e**	EtOAc	120	18	2.4/1	95
15	**25e**	CH_2Cl_2	192	74	8/1	91
16	**25e**	toluene	120	27	2.9/1	90

[a]2 equiv. of crotonolactone. [b]20 mol%. [c] ^{1}H NMR of crude products. [d]Chiral HPLC analysis. [e]'−ee' indicates formation of the enantiomer of **28** [f]Reaction at 0 ^oC

Table 4.1. Optimization of the ODVA reaction of crotonolactone and aldehyde **27**.

Thus the direct vinylogous aldol reaction of γ-crotonolactone with the aldehyde **27** using **25e** as the catalyst provided the butenolide **28** in good yield and diastereoselectivity (74%, *anti*/*syn* = 8/1) and excellent enantiomeric excess (er = 19/1 for the *anti* diastereomer) when the reaction was conducted in dichloromethane (Scheme 4.4). Following the planned synthetic strategy (Figure 4.2), it may be noted that the 2,3-*trans* substitution in the target piperidine can be obtained only from the *anti* diastereomer of the corresponding amino butyrolactone (Figure 4.2, **E**). Since our approach to this amino lactone would involve an invertive amination of the precursor alcohol, a switch of the aldol product stereochemistry from the *anti* to the *syn* isomer is required. For this, **28** was first hydrogenated and then Mitsunobu inversion of the secondary alcohol was examined under a variety of conditions. These attempts invariably led to complex mixtures and hence an alternate strategy for alcohol inversion became necessary. Accordingly, the alcohol was first oxidized to provide the ketolactone **29**. Reduction of **29** with K-Selectride® gave *syn*-**30** (70%) with good diastereoselectivity (*syn*/*anti* = 16/1, presumably *via* the Felkin-Anh model,[15] **G**, Scheme 4.4).[16]

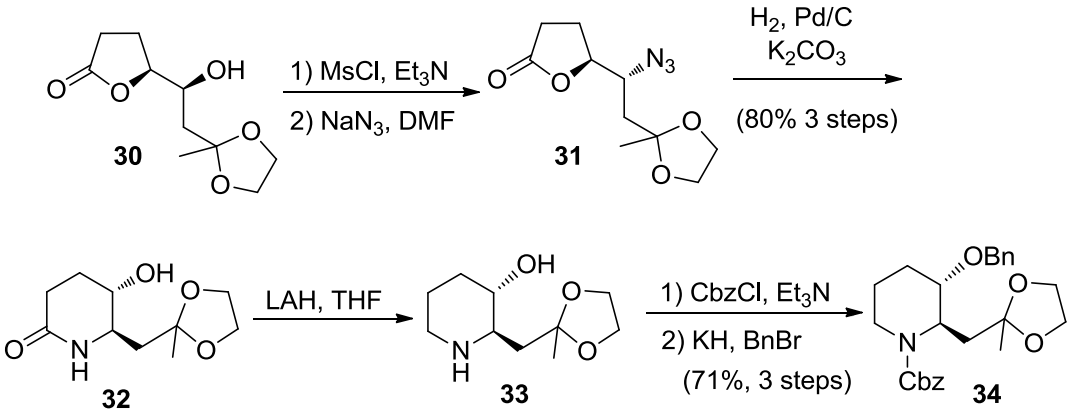


Scheme 4.4. Synthesis of *syn*-alcohol **30** *via* ODVA reaction.

The stereochemical assignments for **28** were based on our earlier studies of the organocatalytic vinylogous aldol reaction of γ-crotonolactone in which aromatic aldehydes provided the *anti* aldol as the major product (Chapter 2, pages 34-36). For the *anti* and *syn* assignments in the present study**,** the trend in chemical shifts of the methine protons (CH-O) in these aldol products were compared with those observed for **28** (see ref. 10d). The formation of (+)-febrifugine in the present study confirms the absolute configuration of **28**.

The lactone **30** was readily converted into the azido lactone **31** (mesylation and azidation with inversion) with the required *anti* stereochemistry (*anti*/*syn* = 16/1, Scheme 4.5). Reduction of the azide (H_2, Pd/C) generated a mixture of the corresponding amino butyrolactone and the required piperidone **32** obtained from the intramolecular *N*-acylation of the amino lactone. Notably, hydrogenation of **31** in the presence K_2CO_3

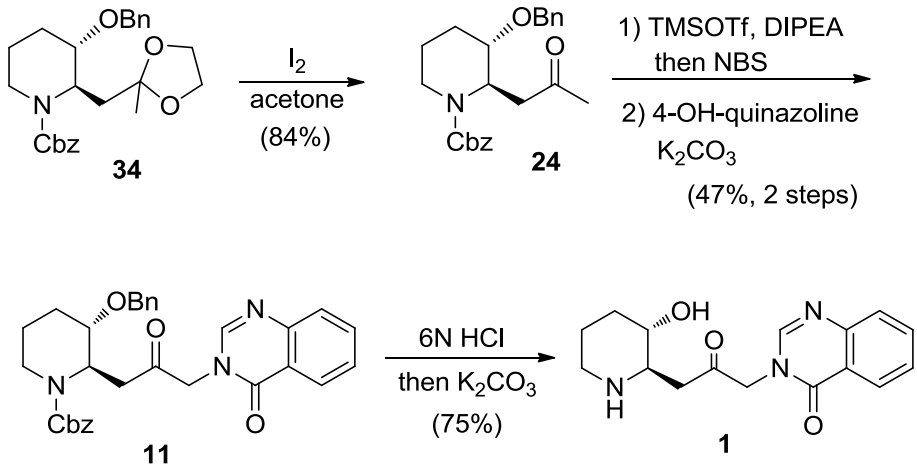
significantly facilitated this rearrangement to directly provide **32** (80% from **30**) without any residual amino lactone. Reduction of the lactam in **32** provided the corresponding piperidine **33** which was isolated as a single diastereomer, presumably due to enrichment of the *trans* isomer during the reduction and isolation. *N*-protection of the piperidine **33** as carbobenzyloxy followed by protection of hydroxyl group as benzyl ether to provide the key intermediate **34** (71% from **32**, Scheme 4.5).



Scheme 4.5. Synthesis of piperidine **34**.

With the piperidine **34** in hand, the final steps of the synthesis were initiated. The ketone in **34** was unmasked by treatment of the ketal with iodine in acetone to provide **24** (Scheme 4.6). Comparison of the spectral data of **24** with reported values[3a,i] confirmed the *trans* orientation of the substituents on the piperidine ring. This also confirms the initial stereochemical assignments for **28**. Bromination of the ketone in **24** was achieved by the procedure reported by Honda (TMSOTf, DBU then NBS)[3i] and the crude bromoketone was reacted with 4-hydrazoquinazoline to provide the protected febrifugine

derivative **11**. Deprotection of **11** (6 N HCl) and subsequent neutralization provided (+)-febrifugine. ($[\alpha]_D^{23}$ = +17.7 (*c* 0.6, EtOH); lit.[3a] $[\alpha]_D^{25}$ = +14.6 (*c* 1.0, EtOH), 86% ee).



Scheme 4.6. Total synthesis of (+)-febrifugine.

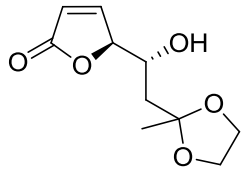
4.4 Conclusions

In conclusion, a stereoselective synthesis of (+)-febrifugine (14 steps, 6.8% overall yield) was achieved by employing an organocatalytic asymmetric direct vinylogous aldol reaction of γ-crotonolactone and the isomerization of a 2-aminoalkyl furanone to the 2,3-disubstituted piperidine core of the target as the key steps. Since the bromoketone obtained from **24** can be converted into (+)-halofuginone by coupling with 7-bromo-6-chloro-4-hydroxyquinazoline,[3a] the present study also constitutes a formal synthesis of (+)-halofuginone.

4.5 Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230-400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

(*S*)-5-[(*R*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(5H)-one (28):

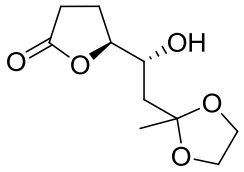


A mixture of the catalyst **25e** (20 mol %, 1.17 g), the aldehyde **27** (1.40 g, 10.8 mmol) and 2-(5H)-furanone **26** (1.50 mL, 21.5 mmol) in dichloromethane (10.0 mL) was stirred for 192 h at ambient temperature. The mixture was diluted with ethyl acetate (100 mL), filtered and the filtrate was concentrated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 10/1) to provide 1.73 g (74%) of **28** as a pale yellow solid (*anti*/*syn* = 8/1 as determined by ^{1}H NMR analysis of the crude product).

IR (neat): 3467, 2988, 2889, 1795, 1748, 1378, 1163, 1104, 1034, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 7.67 (dd, 1H, *J* = 5.8, 1.5 Hz), 6.18 (dd, 1H, *J* = 5.8, 1.9 Hz), 4.85 (dt, 1H, *J* = 7.0, 1.7 Hz), 4.04-3.99 (m, 4H), 3.88 (ddd, 1H, *J* = 10.1,

7.0, 2.0 Hz), 3.83 (s, 1H), 2.18 (dd, 1H, *J* = 14.6, 1.9 Hz), 1.95-1.89 (m, 1H), 1.37 (s, 3H); **Visible resonances for the *syn* diastereomer:** δ 7.52 (dd, 1H, *J* = 5.7, 1.5 Hz), 6.19 (part of dd, 1H), 5.04-5.02 (m, 1H), 4.28-4.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 172.8, 154.9, 122.1, 110.0, 85.2, 69.6, 64.7, 64.3, 41.4, 24.1; **Visible resonances for the *syn* diastereomer:** δ 172.9, 153.8, 122.7, 109.8, 84.9, 67.4, 64.8, 64.3, 40.1, 24.0; MS (APCI, pos.): *m/z* 215.1 (M+1); HRMS (CI): 215.0915 (215.0919 calcd for $C_{10}H_{15}O_5$ (M+H)); R_f = 0.30 (EtOAc/hexanes, 4/1); Ee: 90% (*anti*); HPLC: Chiralpak AS-H, hexanes/2-propanol 92/8, 210 nm, *anti* **28**: 42.4 min (minor), 76.7 min (major); *syn* **28**: 57.9 min (major), 83.1 min (minor). In repeated runs *anti* **28** was obtained in 89-93% ee.

(*S*)-5-[(*R*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]dihydrofuran-2(3H)-one (28a):

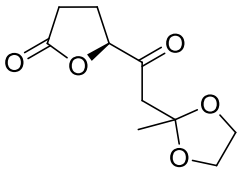


Pd/C (10%, 340 mg) was added to a stirred solution of **28** (1.70 g, 7.93 mmol) in methanol (80.0 mL). The mixture was stirred for 16 h at ambient temperature under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with methanol (2 x 30 mL) and the combined filtrates were concentrated under reduced pressure to provide 1.70 g (99%) of (*S*)-dihydro-5-[(*R*)-1-hydroxy-2-(2-methyl-

1,3-dioxolan-2-yl)ethyl]furan-2(3H)-one **28a** as a white solid (*anti*/*syn* = 8/1). This was pure (^{1}H NMR) and was directly used in the next step.

IR (neat): 3500, 2985, 2892, 1770, 1658, 1567, 1549, 1459, 1377, 1278, 1190, 1171, 1119, 1027, 996 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 4.37-4.32 (m, 1H), 4.06-3.99 (m, 5H), 3.58 (br s, 1H), 2.60 (ddd, 1H, *J* = 17.8, 9.4, 6.4 Hz), 2.53-2.48 (m, 1H), 2.28-2.23 (m, 1H), 2.01 (dd, 1H, *J* = 14.6, 2.0 Hz), 1.81 (dd, 1H, *J* = 14.6, 10.0 Hz), 1.38 (s, 3H); **Visible resonances for the *syn* diastereomer:** δ 4.43-4.40 (m, 1H), 2.68-2.64 (m, 1H), 2.46-2.45 (m, 1H), 2.08 (dd, 1H, *J* = 14.9, 10.5 Hz), 1.87 (dd, 1H, *J* = 14.8, 1.8 Hz), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 177.2, 110.0, 82.3, 69.1, 64.8, 64.3, 40.9, 28.3, 24.2, 22.8; **Visible resonances for the *syn* diastereomer:** δ 177.9, 109.9, 82.4, 69.8, 68.5, 64.8, 40.8, 28.3, 24.0, 23.9; MS (APCI, pos.): *m/z* 217.1 (M+1); HRMS (CI): 217.1072 (217.1076 calcd for $C_{10}H_{17}O_5$ (M+H)); R_f = 0.30 (EtOAc/hexanes, 3/2).

(*S*)-5-[2-(2-methyl-1,3-dioxolan-2-yl)acetyl]dihydrofuran-2(3H)-one (29):

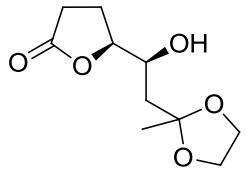


To a solution of the above alcohol **28a** (900 mg, 4.16 mmol) in CH_2Cl_2 (30.0 mL) was added Dess-Martin periodinane (3.53 g, 8.32 mmol) and the mixture was stirred at room temperature for 16 h. Saturated aqueous sodium bicarbonate (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30

mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 1/1) to provide 714 mg (80%) of **29** as a pale yellow liquid.

IR (neat): 2996, 2893, 1769, 1718, 1373, 1252, 1153, 1043, 995, 947, 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 4.91-4.88 (m, 1H), 3.99-3.95 (m, 4H), 3.09 (d, 1H, *J* = 13.4 Hz), 2.88 (d, 1H, *J* = 13.4 Hz), 2.55-2.45 (m, 3H), 2.38-2.33 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0, 176.3, 108.0, 82.2, 64.8, 64.7, 47.5, 27.3, 24.7, 24.2; MS (APCI, pos.): *m/z* 215.1 (M+1), $[\alpha]_D^{23}$ = +18.8 (*c* 0.92, $CHCl_3$); HRMS (CI): *m/z* 214.0808 (214.0841 calcd for $C_{10}H_{14}O_5$); R_f = 0.30 (EtOAc/hexanes, 1/1).

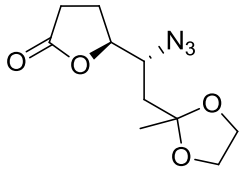
(*S*)-5-[(*S*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(5H)-one (30):



K-Selectride® (1.0 M in THF, 2.80 mL, 2.80 mmol) was added to a stirred solution of the ketone **29** (400 mg, 1.86 mmol) in THF (2.0 mL) at -78 ^oC and the mixture was stirred at -78 ^oC for 1 h. Saturated aqueous ammonium chloride solution (15 mL) was added followed by EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 1/1) to provide 283 mg (70%) of **30** as a colorless liquid (*syn*/*anti* = 16/1).

IR (neat): 3498, 2986, 2960, 2933, 2890, 1765, 1378, 1260, 1167, 1110, 1038, 913, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 4.44-4.39 (m, 1H), 4.02-4.01 (m, 4H), 4.00-3.95 (m, 1H), 3.57 (br s, 1H), 2.74-2.63 (m, 1H), 2.50-2.39 (m, 1H), 2.31-2.25 (m, 2H), 2.15-2.02 (m, 1H), 1.87 (dd, 1H, *J* = 14.8, 1.8 Hz), 1.38 (s, 3H); **Visible resonances for the *anti* diastereomer:** δ 4.43-4.40 (m, 1H), 2.68-2.64 (m, 1H), 1.87 (dd, 1H, *J* = 14.6, 2.0 Hz), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ***Syn* diastereomer:** δ 177.9, 109.9, 82.4, 69.8, 64.8, 64.3, 40.8, 28.3, 24.1, 23.9; **Visible resonances for the *anti* diastereomer:** δ 177.2, 110.0, 82.2, 69.1, 64.8, 40.9, 28.3, 24.2, 22.8; MS (APCI, pos.): *m/z* 217.1 (M+1); HRMS (CI): 217.1072 (217.1076 calcd for $C_{10}H_{17}O_5$ (M+H)); R_f = 0.30 (EtOAc/hexanes, 3/2).

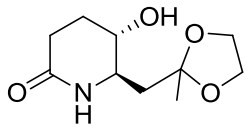
(*S*)-5-[(*R*)-1-Azido-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-dihydrofuran-2(3H)-one (31):



To a solution of **30** (600 mg, 2.77 mmol) in CH_2Cl_2 (10.0 mL) at 0 ^oC under nitrogen was added triethylamine (463 µL, 3.32 mmol) followed by methanesulfonyl chloride (259 µL, 3.32 mmol). The mixture was stirred for 1 h at 0 ^oC and water was added at 0 ^oC. The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 810 mg (99%) of the mesylate as a yellow oil. This was used immediately in the next step without purification.

Sodium azide (822 mg, 12.6 mmol) was added to a solution of the crude mesylate (744 mg, 2.53 mmol) in DMF (8.0 mL) and the mixture was stirred at 80 ^{o}C for 96 h under N_2. The mixture was cooled to room temperature and EtOAc (30 mL) was added followed by water (30 mL). The resulting biphase was separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to provide 610 mg (quant.) of **31** as a yellow oil (*anti*/*syn* = 16/1). This was pure (^{1}H NMR) and was directly used in the next step. An analytical sample (*anti*/*syn* = 25/1) was obtained by flash column chromatography on silica gel (hexanes/EtOAc, 7/3). IR (neat): 2987, 2959, 2923, 2852, 2108, 1772, 1462, 1378, 1255, 1186, 1144, 1029, 948 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 4.56-4.4.52 (m, 1H), 4.04-3.96 (m, 4H), 3.94-3.91 (m, 1H), 2.63 (ddd, 1H, *J* = 17.9, 10.2, 5.5 Hz), 2.55-2.48 (m, 1H), 2.27-2.19 (m, 1H), 2.15-2.07 (m, 1H), 1.94 (dd, 1H, *J* = 14.9, 7.3 Hz), 1.88 (dd, 1H, *J* = 14.9, 4.5 Hz), 1.37 (s, 3H); **Visible resonances for the *syn* diastereomer:** δ 4.60-4.57 (m, 1H), 3.58-3.54 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ***Anti* diastereomer:** δ 176.5, 108.1, 80.9, 64.7, 64.5, 60.5, 39.3, 28.2, 24.3, 22.2; **Visible resonances for the *syn* diastereomer:** δ 176.4, 108.2, 81.8, 64.64, 64.61, 60.5, 39.2, 28.1, 24.5, 22.4; MS (CI pos.): *m/z* 242.1 (M+1); HRMS (APCI pos.): *m/z* 242.1145 (242.1141 calcd for $C_{10}H_{16}N_3O_4$ (M+H)); R_f = 0.50 (EtOAc/hexanes, 3/2).

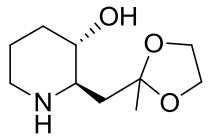
(5*S*,6*R*)-5-Hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidin-2-one (32):



To a stirred solution of the azide **31** (281 mg, 1.16 mmol) in methanol (5.0 mL) at ambient temperature was added K_2CO_3 (56 mg, 20%) followed by Pd/C (10%, 56 mg). The mixture was stirred for 16 h at ambient temperature under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 x 20 mL) and the combined filtrates were concentrated under reduced pressure to provide a yellow gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 19/1) to provide 200 mg (80%) of **32** as a white solid (*trans*/*cis* = 17/1). The overall yield of **32** (from **30**) is 80%.

IR (neat): 3352, 3229, 1633, 1464, 1420, 1384, 1255, 1215, 1173, 1129, 1064, 1029, 988, 947, 902, 855 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): ***Trans* diastereomer:** 6.63 (br s, 1H), 4.01-3.97 (m, 4H), 3.56 (br t, 1H, *J* = 9.5 Hz), 3.43-3.39 (m, 1H), 2.86 (br s, 1H), 2.49 (ddd, 1H, *J* = 18.0, 6.2, 3.4 Hz), 2.38 (ddd, 1H, *J* = 17.9, 11.4, 6.4 Hz), 2.32 (dd, 1H, *J* = 14.5, 2.1 Hz), 2.08-2.03 (m, 1H), 1.89-1.83 (m, 1H), 1.73 (dd, 1H, *J* = 14.5, 9.8 Hz), 1.35 (s, 3H); **Visible resonances for the *cis* diastereomer:** 6.47 (s, 1H), 3.67-3.64 (m, 1H), 2.01-1.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): ***Trans* diastereomer:** δ 170.9, 109.7, 68.9, 64.7, 64.3, 55.5, 41.8, 29.1, 29.0, 24.0; **Visible resonances for the *cis* diastereomer:** δ 171.5, 109.4, 65.7, 64.6, 53.1, 40.5, 27.6, 25.8, 24.2; MS (APCI, pos.) *m/z* 216.1 (M+1); HRMS (CI): 216.1235 (216.1236 calcd for $C_{10}H_{18}NO_4$ (M+H)); R_f = 0.25 (CH_2Cl_2/MeOH, 4/1).

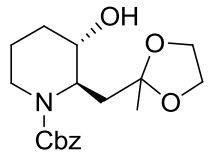
(2*R*,3*S*)-Benzyl-3-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (33):



To a stirred suspension of $LiAlH_4$ (101 mg, 2.66 mmol) in THF (5.0 mL) was added **32** (0.19 g, 0.88 mmol) dissolved in THF (5.0 mL) and the mixture was heated to reflux for 24 h. The mixture was cooled to 0 ^oC, water (0.50 mL) was added slowly and the mixture was stirred for 20 min. at room temperature. Sodium sulfate (1.0 g) was added to the mixture and it was stirred for 10 min. The mixture was then filtered through a pad of Celite. The filter cake was washed with EtOAc (3 x 20 mL) and the combined filtrates were concentrated under reduced pressure to provide 160 mg (90%) of (2*R*,3*S*)-2-((2-Methyl-1,3-dioxolan-2-yl)methyl)piperidin-3-ol **33** as a white solid. This was exclusively the *trans* diastereomer (500 MHz ^1H NMR) and was used in the next step without purification.

IR (neat): 3316, 3122, 2928, 2862, 2824, 1439, 1374, 1252, 1117, 1086, 1036, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.01-3.96 (m, 4H), 3.20 (ddd, 1H, *J* = 13.1, 8.7, 4.4 Hz), 2.96-2.92 (m, 1H), 2.55 (td, 1H, *J* = 11.8, 2.7 Hz), 2.49 (ddd, 1H, *J* = 11.0, 7.3, 3.7 Hz), 2.23 (dd, 1H, *J* = 14.8, 3.7 Hz), 2.09-2.04 (m, 1H), 1.72 (dd, 1H, *J* = 14.8, 7.2 Hz), 1.68-1.66 (m, 1H), 1.54-1.50 (m, 1H), 1.38 (s, 3H), 1.35-1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.1, 72.2, 64.6, 64.4, 59.9, 46.1, 42.2, 34.2, 25.4, 24.1; MS (APCI, pos.): *m/z* 202.1 (M+1); HRMS (CI): 200.1287 (200.1287 calc. for $C_{10}H_{18}NO_3$ (M-H)), 202.1444 (202.1443 calcd for $C_{10}H_{20}NO_3$ (M+H)); R_f = 0.30 (CH_2Cl_2/MeOH, 4/1).

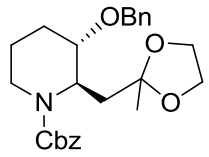
(2*R*,3*S*)-Benzyl 3-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (33a):



To a solution of the above amino alcohol **33** (0.16 g, 0.79 mmol) in CH_2Cl_2 (10.0 mL) were added benzylchloroformate (0.11 mL, 0.79 mmol), and triethylamine (0.13 mL, 0.95 mmol) at 0 ^oC. The solution was stirred at room temperature for 16 h, water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc, 2/3) provided 243 mg (91%) of **33a** as colorless oil.

IR (neat): 3467, 2940, 2880, 1672, 1428, 1352, 1257, 1153, 1117, 1077, 1033, 983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.38-7.28 (m, 5H), 5.15 (s, 2H), 4.49 (br s, 1H), 4.07 (br s, 1H), 3.90-3.88 (br m, 5H), 2.89 (br m, 1H), 1.98-1.83 (m, 2H), 1.80 (dd, 1H, *J* = 14.6, 6.1 Hz), 1.74-1.68 (m, 3H), 1.45-1.35 (br m, 1H), 1.32 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 136.9, 128.4, 127.9, 127.8, 109.0, 68.2, 67.2, 64.54, 64.50, 54.0, 39.1, 38.2, 25.7, 23.9, 19.1; MS (APCI, pos.): *m/z* 336.2 (M+1); HRMS (CI): 336.1813 (336.1811 calcd for $C_{18}H_{26}NO_5$ (M+H)); $[\alpha]_D^{23}$ = −20.9 (*c* 0.38, $CHCl_3$); R_f = 0.30 (EtOAc/hexanes, 3/2).

(2*R*,3*S*)-Benzyl-3-(benzyloxy)-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (34):

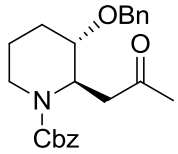


To a solution of the above carbamate **33a** (80 mg, 0.24 mmol) in THF (3.0 mL) under N_2 at room temperature was added potassium hydride (30% dispersion in mineral oil, 32 mg, 0.24 mmol) followed by benzyl bromide (29 µL, 0.24 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 2 h, cooled to 0 ^{o}C and water was added. The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 1/1) to give 87 mg (86%) of **34** as colorless oil.

IR (neat): 2930, 2881, 1692, 1423, 1351, 1255, 1200, 1157, 1090, 1045, 1025, 946 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**: Major rotamer:** δ 7.34-7.24 (m, 10H), 5.11-5.07 (AB system, 2H, *J* = 12.4 Hz), 4.69 (t, 1H, *J* = 5.6 Hz), 4.54 (d, 1H, *J* = 12.2 Hz), 4.43 (d, 1H, *J* = 12.2 Hz), 4.17 (dd, 1H, *J* = 13.5, 3.5 Hz), 3.91-3.82 (m, 3H), 3.74-3.72 (m, 1H), 3.50-3.46 (m, 1H), 2.85 (td, 1H, J = 13.5, 2.9 Hz), 2.04-1.82 (m, 3H), 1.78-1.73 (m, 1H), 1.70-1.62 (m, 2H), 1.25 (s, 3H); **Visible resonances for the minor rotamer:** δ 5.19-5.14 (AB system, 2H, *J* = 12.6 Hz), 4.88 (t, 1H, *J* = 5.8 Hz), 4.73 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.06 (dd, 1H, *J* = 13.4, 3.4 Hz), 3.54-3.52 (m, 1H), 2.91 (td, 1H, J = 13.6, 2.8 Hz), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): **Major rotamer:** δ 155.9, 138.9, 137.0, 128.3, 128.2 (2C), 127.9, 127.7, 127.1, 109.1, 74.5, 69.8, 67.1, 64.5, 64.4, 49.8,

39.1, 38.4, 24.1, 24.0, 19.6; **Visible resonances for the minor rotamer:** δ 155.7, 137.3, 128.4, 127.7, 127.6, 127.3, 109.2, 75.7, 70.1, 66.8, 64.6, 64.4, 48.9, 39.2, 38.0, 24.6, 24.0, 19.9; MS (APCI, pos.): *m/z* 426.2 (M+1); HRMS (CI): 426.2284 (426.2280 calcd for $C_{25}H_{32}NO_5$ (M+H)); $[\alpha]_D^{23}$ = −12.4 (*c* 0.48, $CHCl_3$); R_f = 0.60 (EtOAc/hexanes, 1/1).

(2*R*,3*S*)-Benzyl 3-(benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (24):

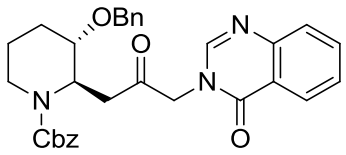


To a solution of **34** (64 mg, 0.15 mmol) in acetone (2.0 mL) was added a solution of iodine (1 mg, 7.8 x 10^{-2} mmol, 5 mol%) in acetone (1.0 mL) at room temperature. The solution was stirred at ambient temperature for 30 min and then concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and aq. 5% $Na_2S_2O_3$ (5 mL) was added. The biphase was stirred vigorously for a few minutes and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 7/3) to provide 48 mg (84%) of **24** as colorless oil.

IR (neat): 2943, 2866, 1689, 1422, 1355, 1254, 1200, 1132, 1050, 959, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)**:** δ 7.32-7.25 (m, 10H), 5.15-5.09 (AB system, 2H, *J* = 12.5 Hz), 5.01 (br s, 1H), 4.65 (br s, 1H,), 4.51 (d, 1H, *J* = 12.0 Hz), 4.13 (br s, 1H), 3.44 (br s, 1H), 2.84 (br s, 1H), 2.69-2.58 (m, 2H), 2.11 (br s, 3H), 1.94-1.85 (m, 2H), 1.65-1.59 (m, 1H), 1.40 (br d, 1H, *J* = 11.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.9, 155.9, 138.6,

136.8, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 73.3, 70.2, 67.2, 49.7, 43.7, 39.5, 30.0, 24.4, 19.5; HRMS (CI): *m/z* 382.2021 (382.2018 calcd for $C_{23}H_{28}NO_4$ (M+H)); $[\alpha]_D^{23}$ = −29.2 (*c* 1.0, $CHCl_3$); lit.[3a] $[\alpha]_D^{25}$ = −26.8 (*c* 1.0, $CHCl_3$) for **24** with 86% ee[3a]; R_f = 0.25 (hexanes/EtOAc, 7/3). The ^1H NMR and ^{13}C NMR data is in agreement with reported data.[3a,3i]

(2*R*,3*S*)-3-Benzyloxy-2-[2-oxoquinazolin-3(4*H*)-yl)propyl]piperidine-1-carbamic acid benzyl ester (11):



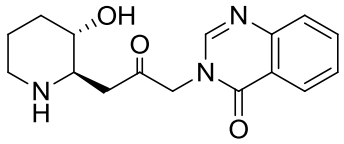
To a solution of **24** (40 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at 0 ^oC was added TMSOTf (40 µL, 0.22 mmol) and DIPEA (42 µL, 0.24 mmol). The resulting mixture was stirred at 0 ^oC for 45 min. and NBS (39 mg, 0.22 mmol) was added. The mixture was stirred at room temperature for 3h and then poured into water (10 mL). The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated to provide the crude bromoketone which was used in the next step without purification.

To a solution of the bromoketone in anhydrous DMF (1.5 mL) was added anhydrous K_2CO_3 (15 mg, 0.11 mmoles) and 4-hydroxyquinazoline (16 mg, 0.11 mmoles). The mixture was stirred at room temperature for 2 h and then poured into water (10 mL). The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and

concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 2/3) to give 27 mg (47%) of **11** as a colorless liquid.

IR: 1726, 1674, 1610, 1424, 1358, 1257, 1085, 1049, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 8.27 (dd, 1H, *J* = 8.0, 1.5), 7.92 (br s, 1H), 7.79-7.73 (m, 2H), 7.52-7.49 (m, 1H), 7.32-7.26 (m, 10H), 5.17 (d, 1H, *J* = 12.4 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 5.01-4.98 (m, 1H), 4.94 (br s, 1H), 4.65-4.63 (m, 1H), 4.53 (br d, 1H, *J* = 11.9 Hz), 4.06 (br s, 1H), 3.52 (br s, 1H), 2.97 (br s, 1H), 2.86 (dd, 1H, *J* = 14.7, 8.7 Hz), 2.78 (br dd, 1H, *J* = 14.7, 6.1 Hz), 1.94-1.88 (br m, 2H), 1.75 (br s, 1H), 1.70-1.63 (m, 1H), 1.44 (apparent br d, 1H, *J* = 12.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 160.9, 156.2, 148.2, 146.5, 138.3, 136.5, 134.5, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 126.7, 121.8, 73.7, 70.4, 67.4, 53.9, 50.6, 41.0, 39.6, 24.3, 19.4; MS (APCI pos.): *m/z* 526.2 (M+1); HRMS (EI+): 525.2285 (525.2264 calcd for $C_{31}H_{31}N_3O_5$ (M+H)) $[\alpha]_D^{23}$ = −24.8 (*c* 1.7, $CHCl_3$); lit. $[\alpha]_D^{25}$ = −22.0 (*c* 1.0, $CHCl_3$)[3m]; R_f = 0.30 (EtOAc); spectroscopic data[3a] (IR, ^{1}H NMR, ^{13}C NMR) and optical rotation[3m] for **11** are in agreement with reported data.[3a,3m]

3-(3-[(2*R*,3*S*)-3-Hydroxypiperidin-2-yl)-2-oxopropyl]quinazolin-4(3*H*)-one ((+)-Febrifugine) (1):



A stirred solution of **11** (17 mg, 0.03 mmol) in aqueous HCl (6 M, 2.0 mL) was heated to reflux for 1 h. The solution was then cooled to 0 ^{o}C and was basified with K_2CO_3 to pH~10. The basic solution was extracted with $CHCl_3$ (3 x 30 mL). The combined organic

layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to provide 10 mg (99%) of crude product. This was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 9/1) to provide 7.5 mg (75%) of (+)-febrifugine as a white solid.

Mp: 133-136 ^oC; (lit.[1] mp 135-138 ^oC). IR (neat): 3306, 3052, 2926, 2851, 2687, 1726, 1669, 1607, 1468, 1361, 1325, 1078, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)**:** δ 8.27 (d, 1H, *J* = 7.9 Hz), 7.91 (s, 1H), 7.78-7.71 (m, 2H), 7.54-7.48 (m, 1H), 4.93-4.80 (AB system, 2H, *J* = 17.5 Hz), 3.30-3.26 (m, 1H), 3.11 (dd, 1H, *J* = 16.0, 4.5 Hz), 2.96 (d, 1H, *J* = 11.9 Hz), 2.88-2.87 (m, 1H), 2.64 (dd, 1H, *J* = 16.1, 7.5 Hz), 2.58 (dt, 1H, *J* = 12., 3.0 Hz), 2.22 (br s, 2H), 2.10-2.06 (m, 1H), 1.74-1.70 (m, 1H), 1.53-1.47 (m, 1H), 1.38-1.30 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7, 161.0, 148.2, 146.4, 134.5, 127.6, 127.4, 126.8, 121.8, 72.2, 60.2, 54.9, 46.0, 44.0, 34.5, 25.6; MS (APCI pos.): *m/z* 302.1 (M+1); HRMS (CI): *m/z* 302.1512 (302.1505 calcd for $C_{16}H_{20}N_3O_3$ (M+H)); $[\alpha]_D^{23}$ = +17.7 (*c* 0.6, EtOH), lit.[3a] $[\alpha]_D^{25}$ = +14.6 (*c* 1.0, EtOH); R_f = 0.20 (CH_2Cl_2/MeOH/Et_3N, 9.00/0.95/0.05). The ^1H NMR and ^{13}C NMR data is in agreement with reported data.[3a,3i]

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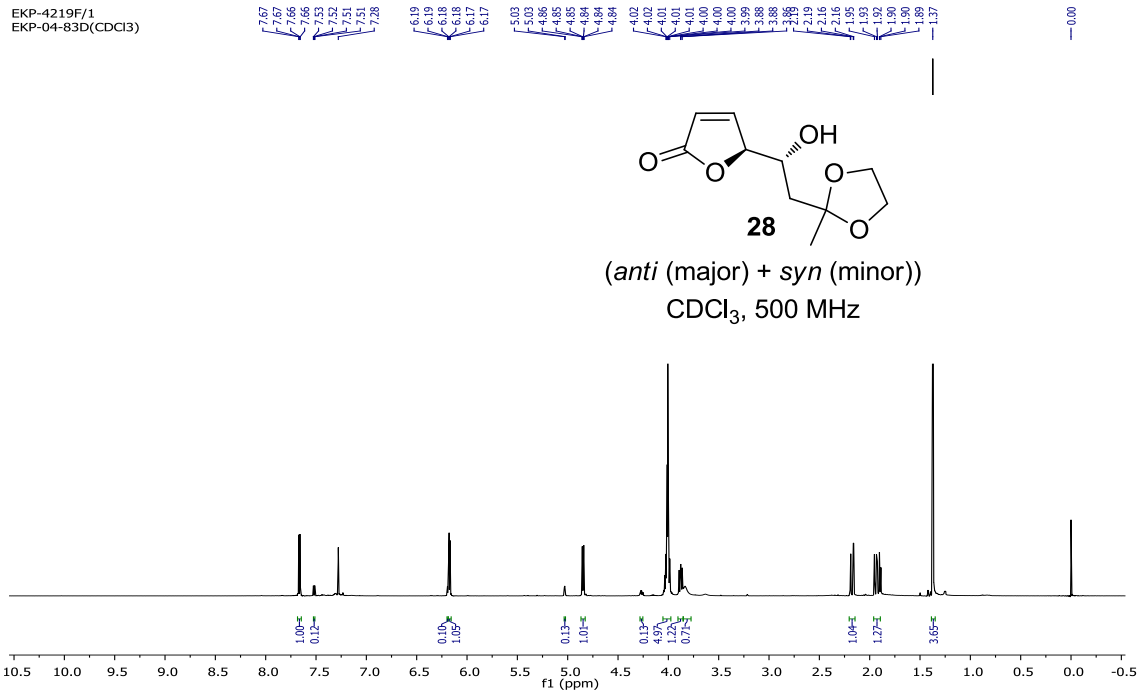
4.7 Selected ^{1}H and ^{13}C NMR spectra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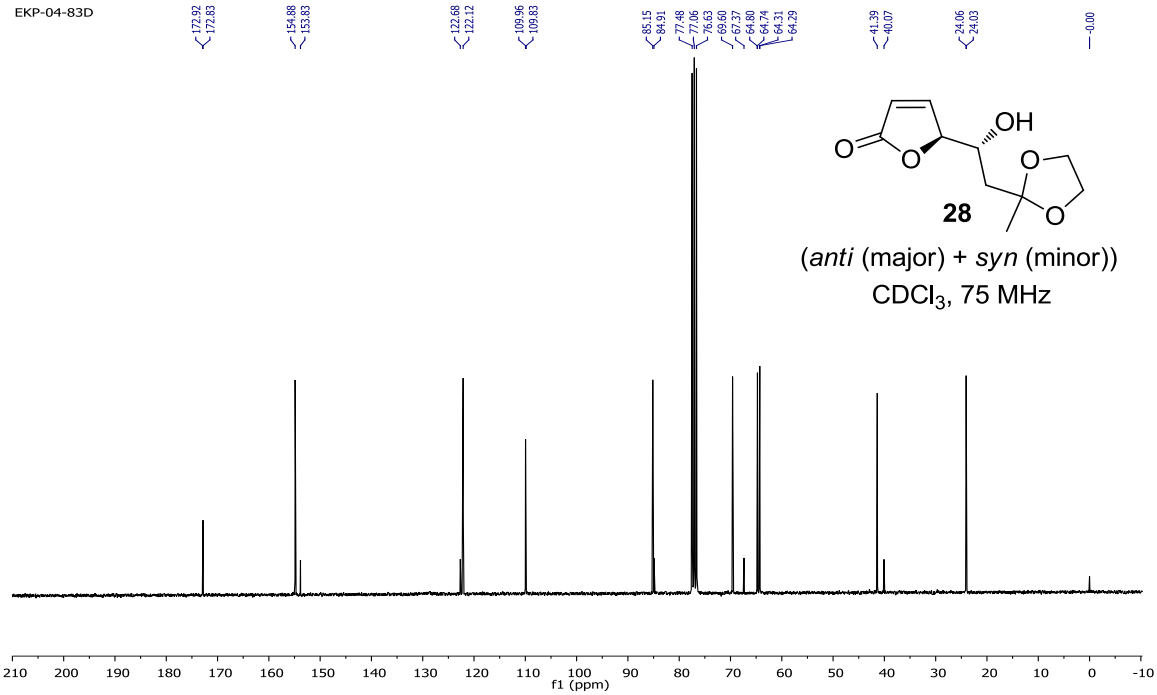
O
O
O
28
(anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)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O
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28
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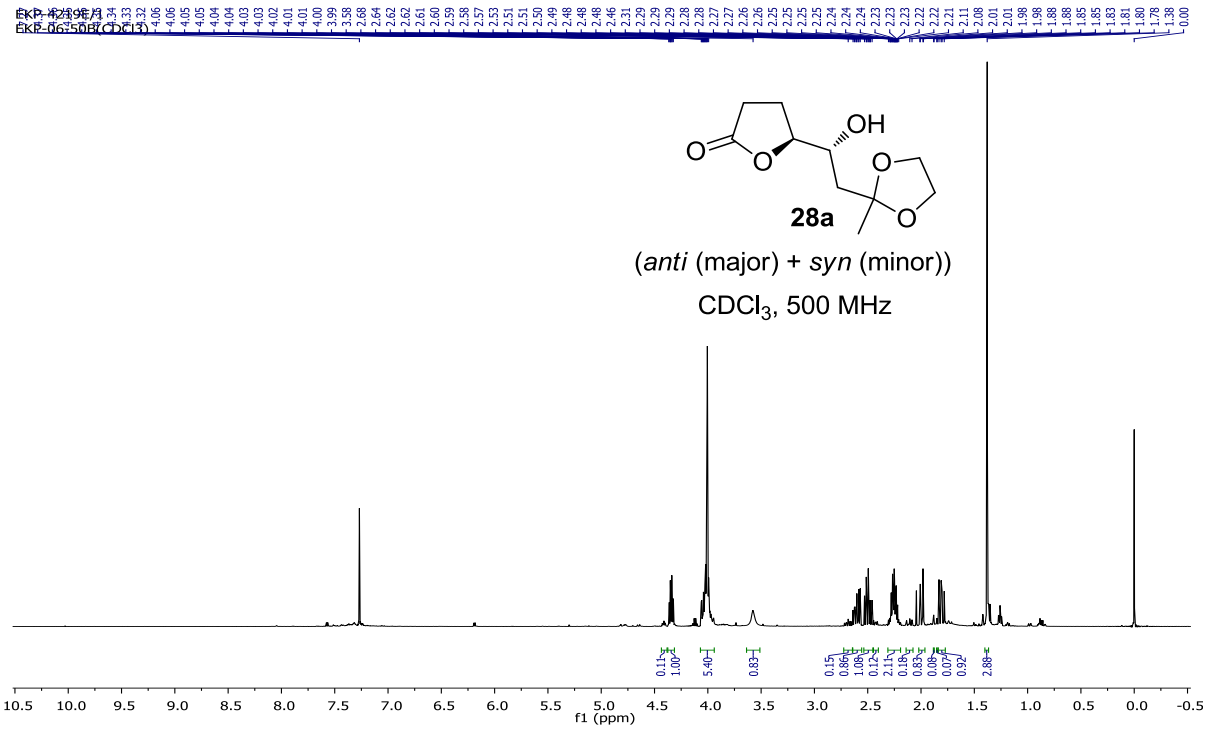
CDCl3, 75 MHz
f1 (ppm)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O
O
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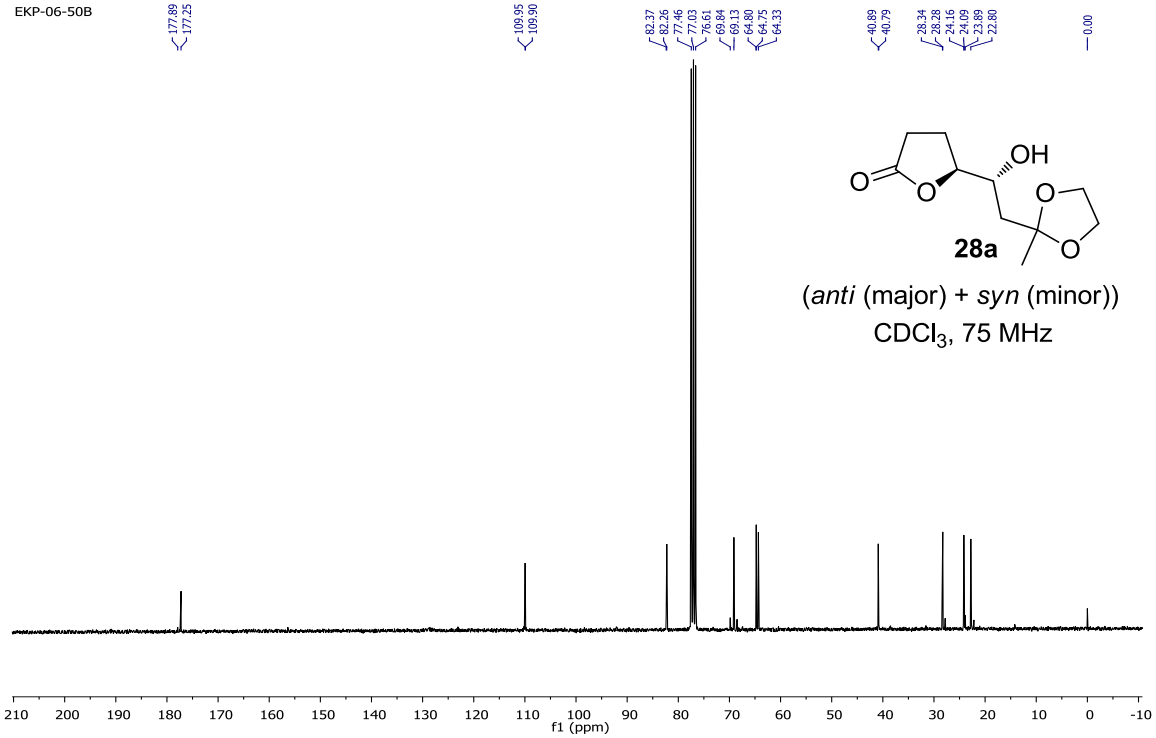
CDCl3, 500 MHz
f1 (ppm)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O
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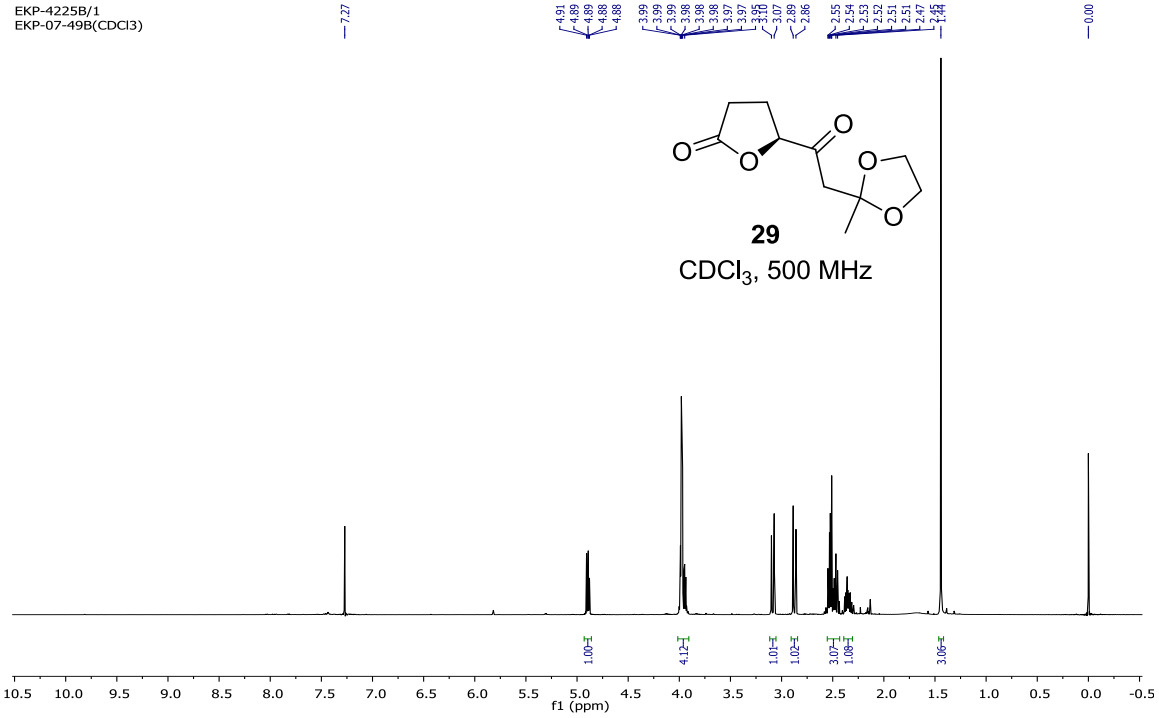
f1 (ppm)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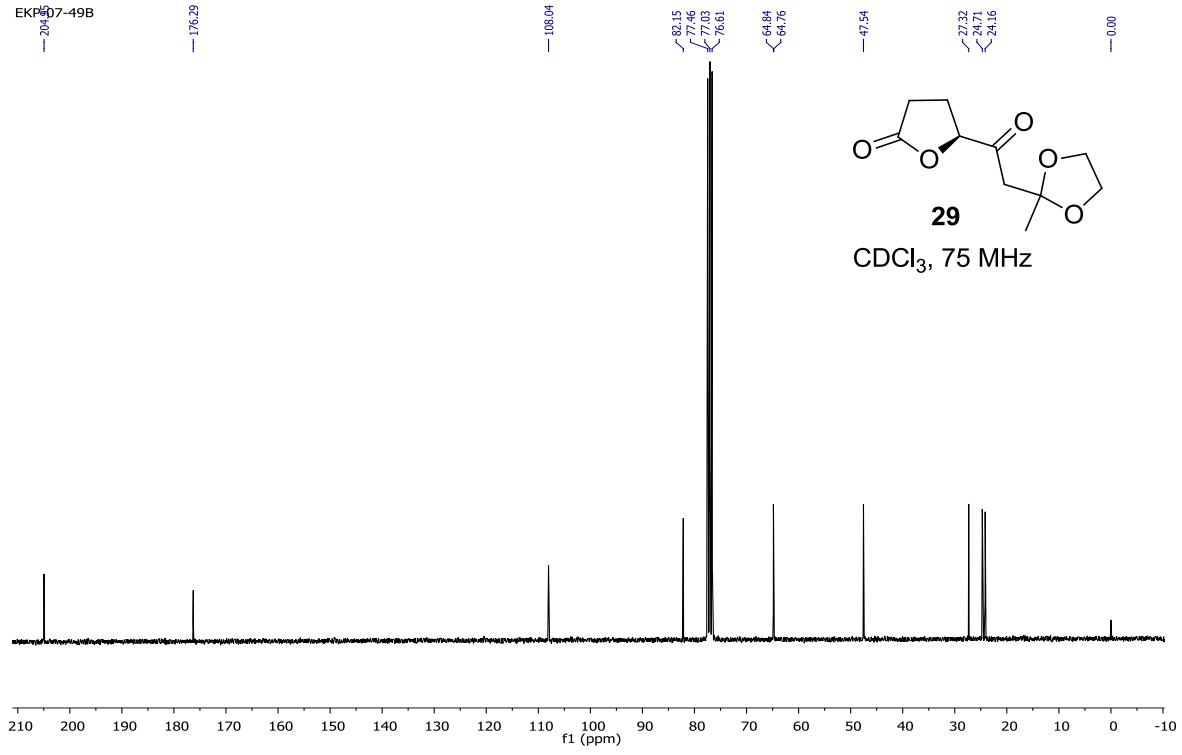
CDCl3, 500 MHz
f1 (ppm)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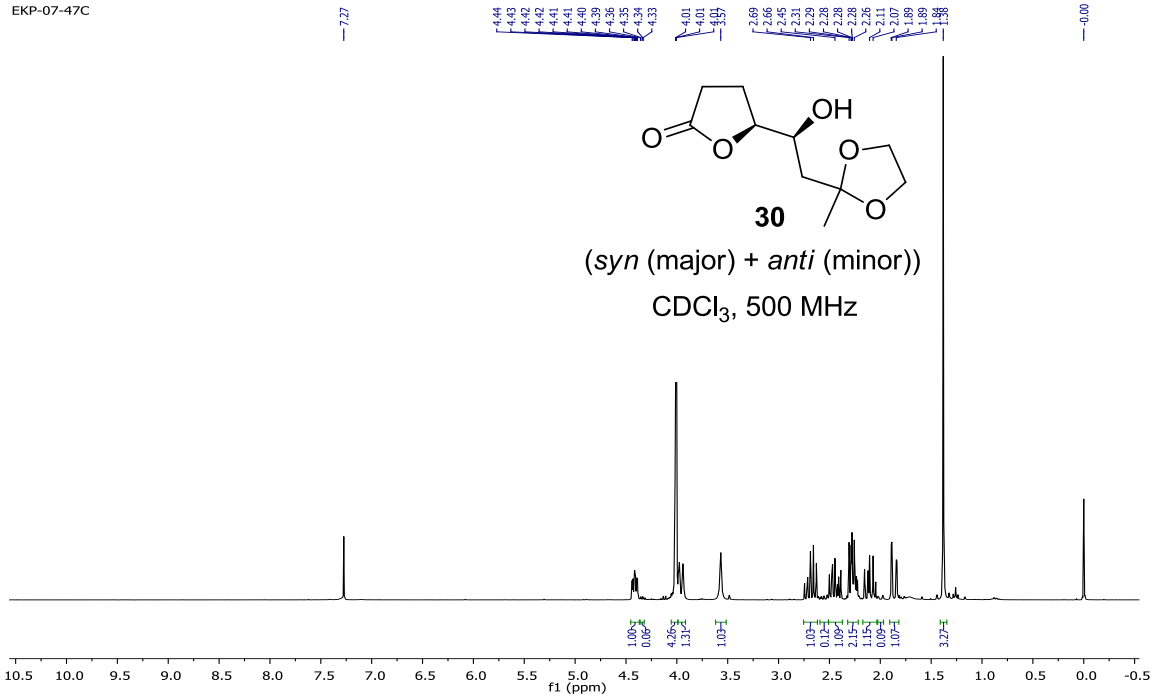
f1 (ppm)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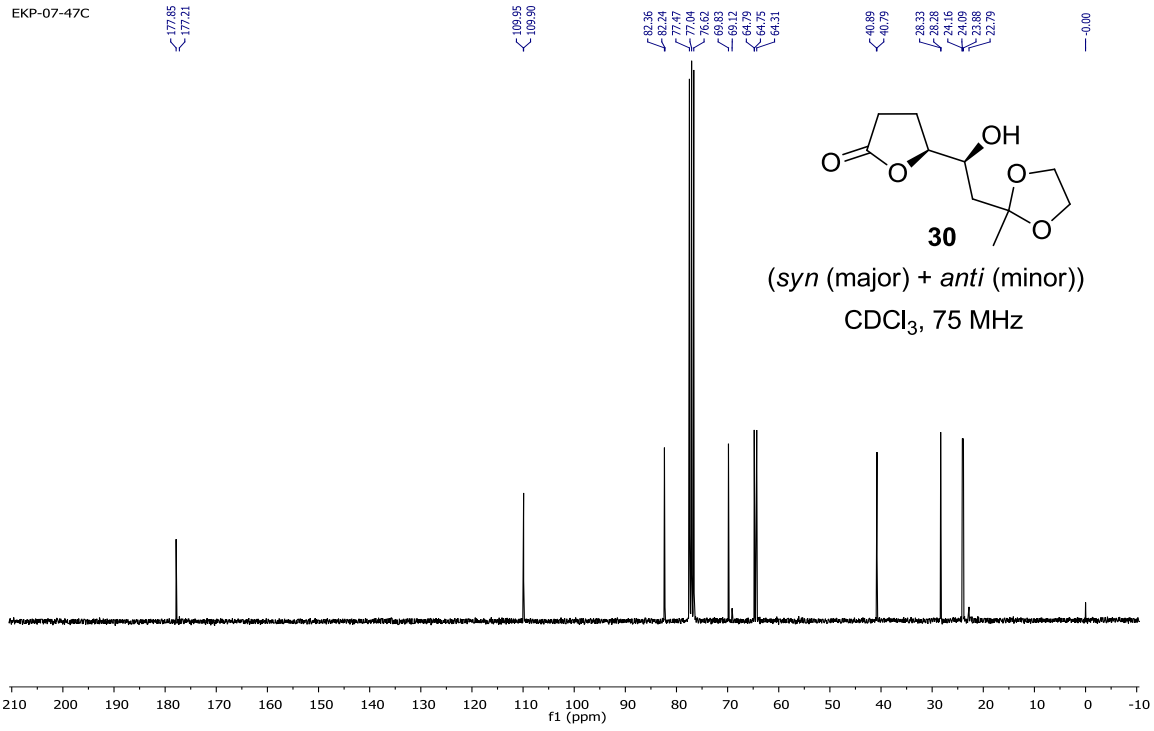
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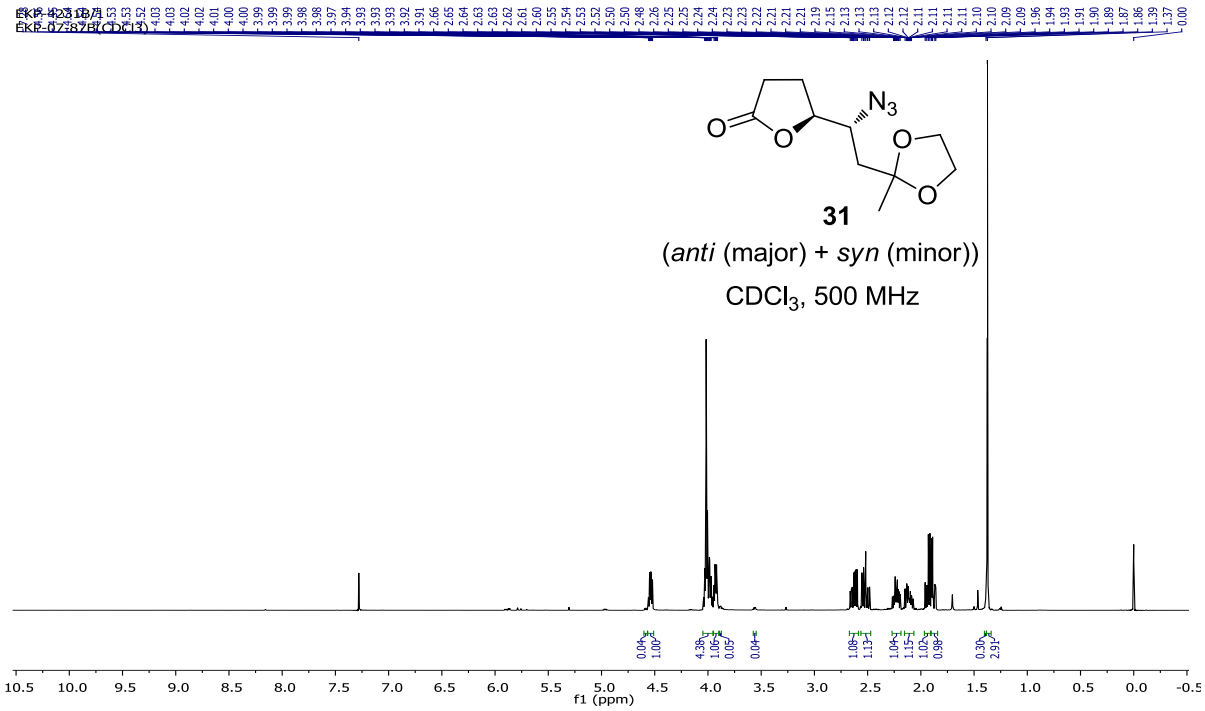
CDCl3, 75 MHz
f1 (ppm)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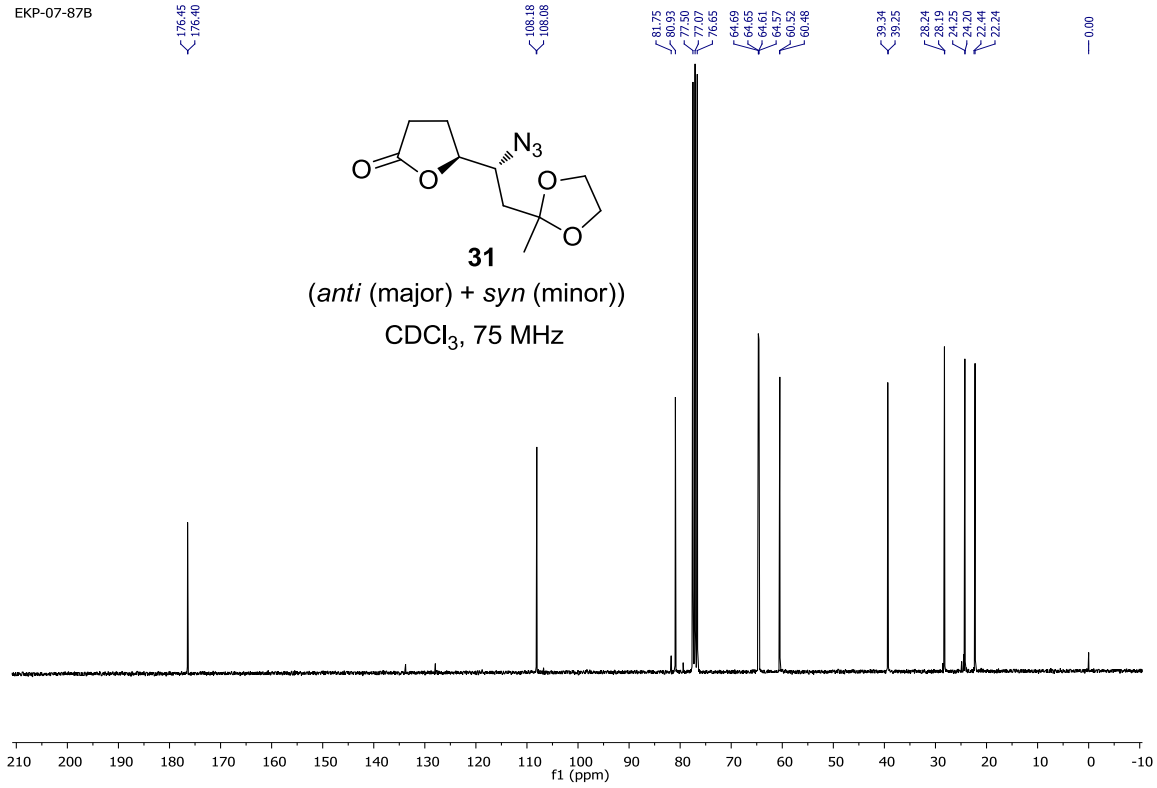
O
O
O
31
(anti (major) + syn (minor))
CDCl3, 500 MHz
f1 (ppm)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O
O
O
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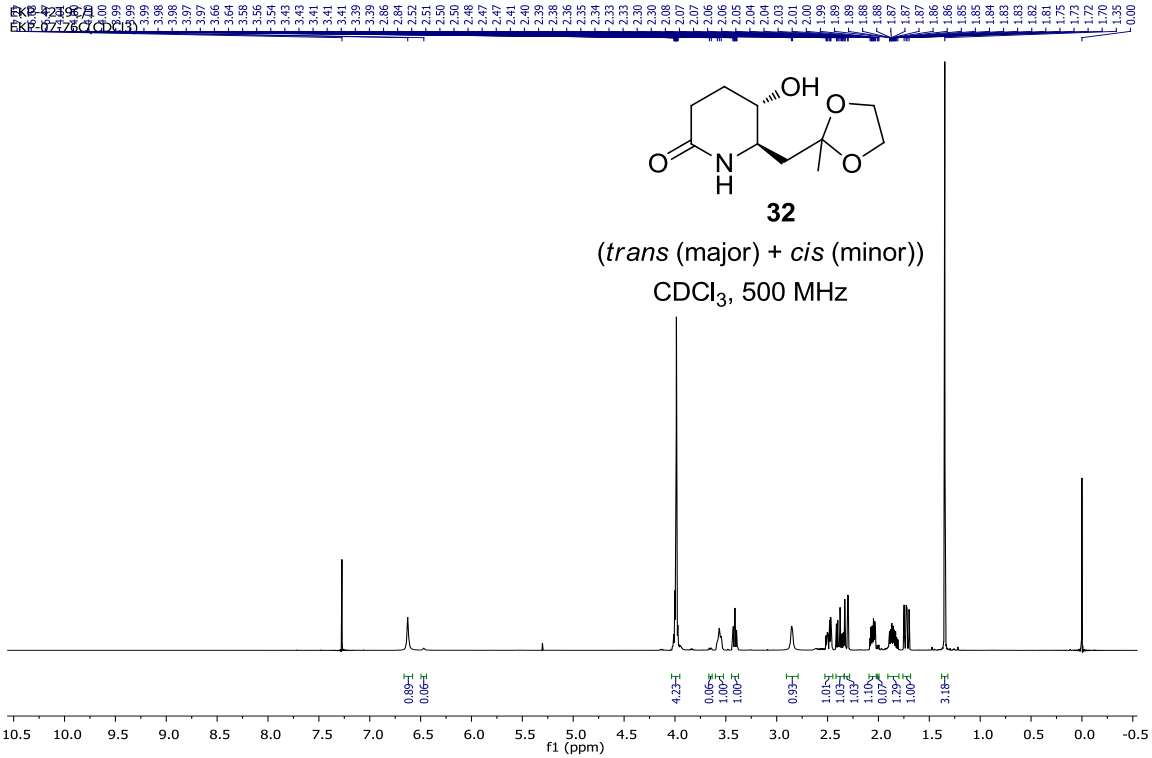
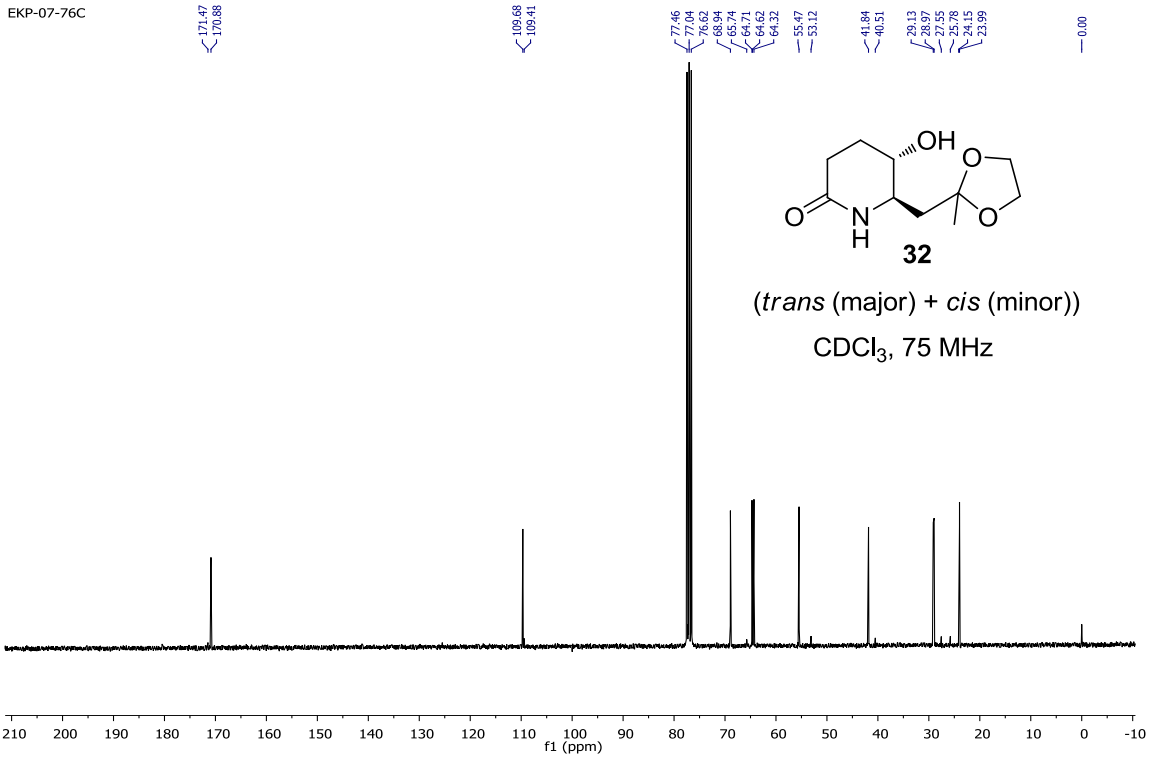
f1 (ppm)


OH
O
O
N
H
O
32
(*trans* (major) + *cis* (minor))
CDCl3, 500 MHz
f1 (ppm)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O
O
N
H
O
32
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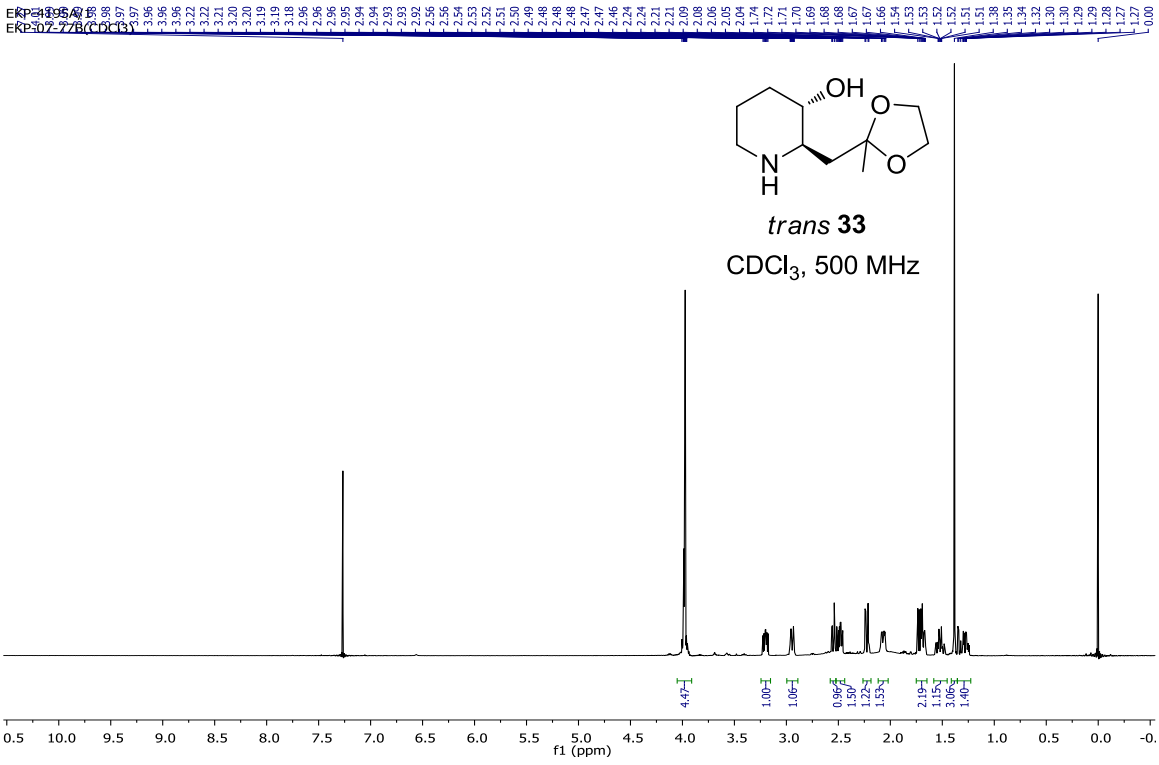
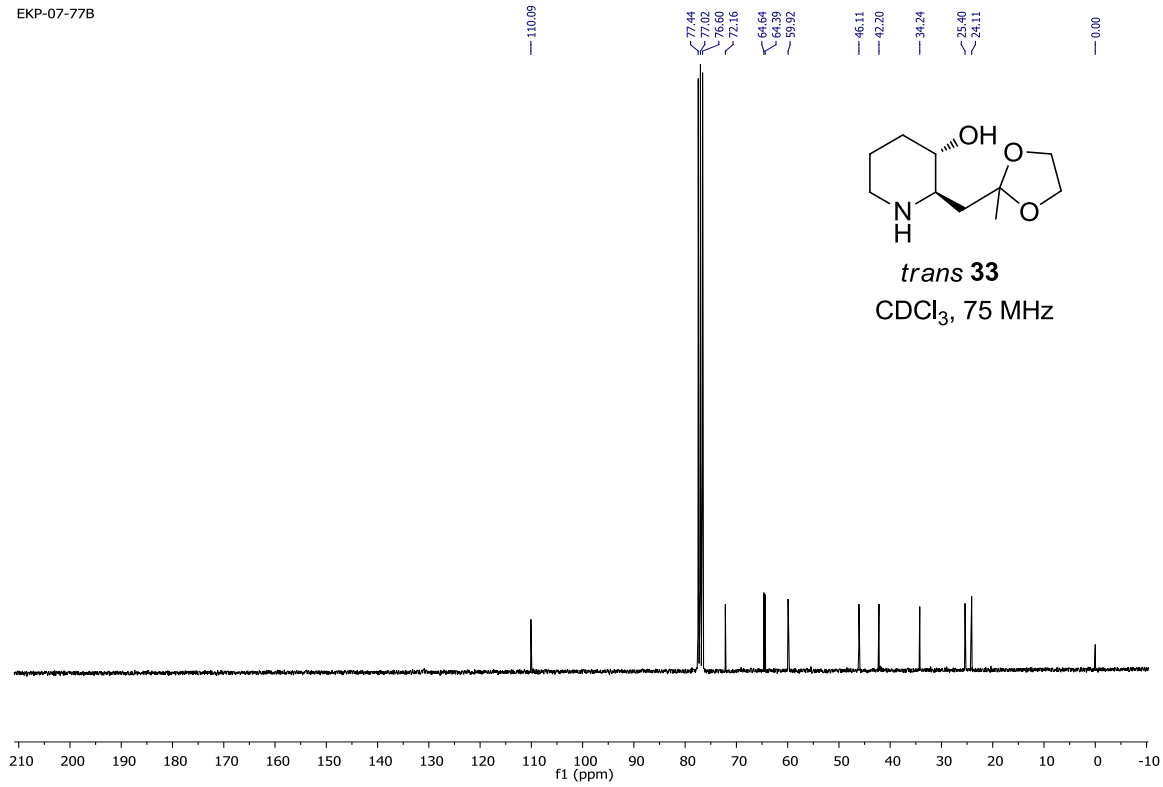
CDCl3, 75 MHz
f1 (ppm)


OH
O
N
H
O
trans 33
CDCl3, 500 MHz
4.47
1.00
1.06
0.96
1.50
1.22
1.53
2.19
1.15
3.06
1.40
f1 (ppm)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110.09
77.44
77.02
76.60
72.16
64.64
64.39
59.92
46.11
42.20
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24.11
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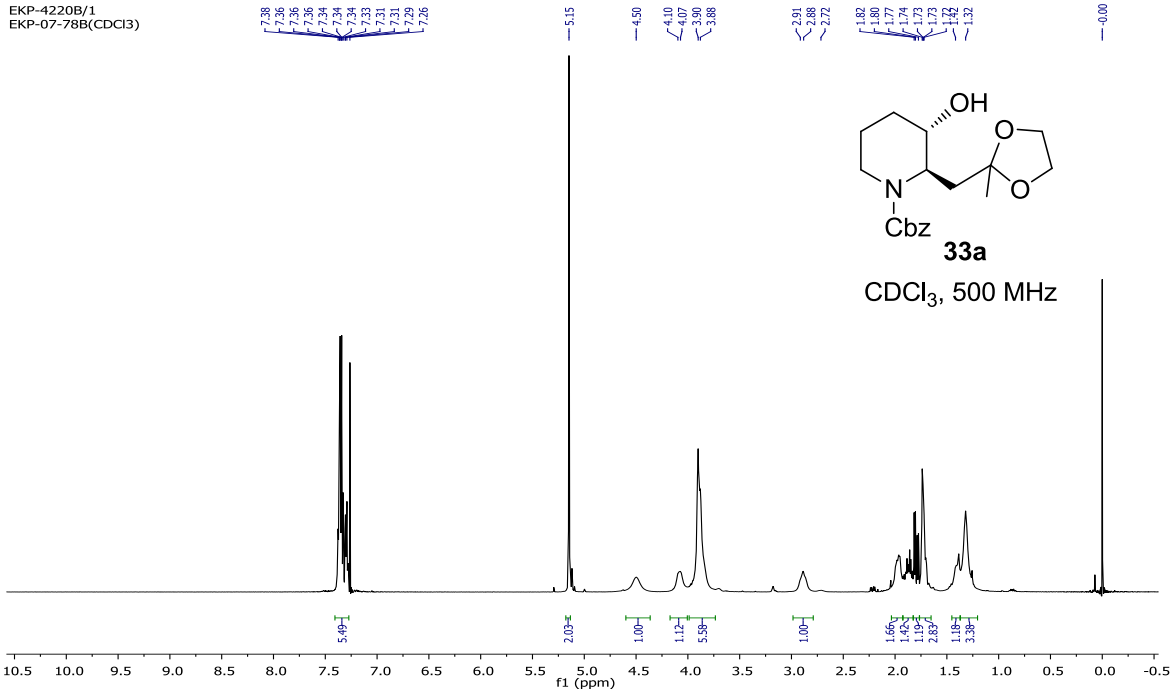
O
trans 33
CDCl3, 75 MHz
f1 (ppm)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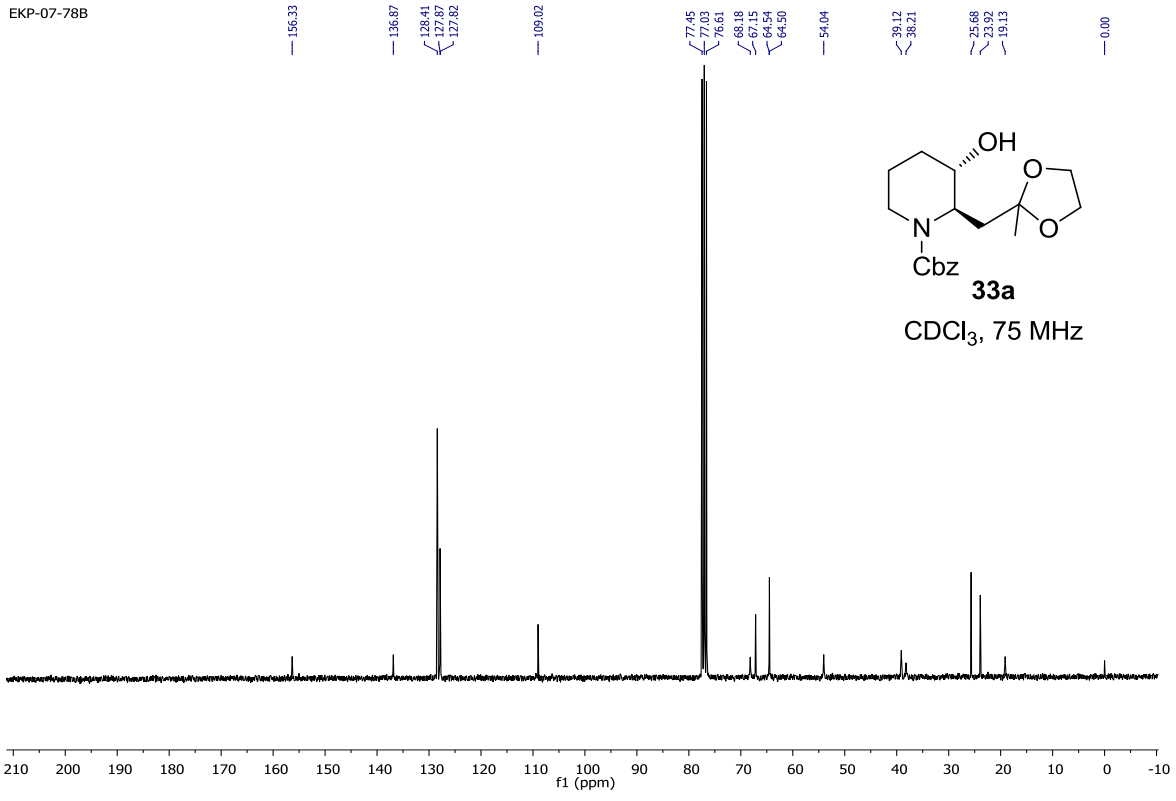
O
N
O
Cbz
33a
CDCl3, 500 MHz
f1 (ppm)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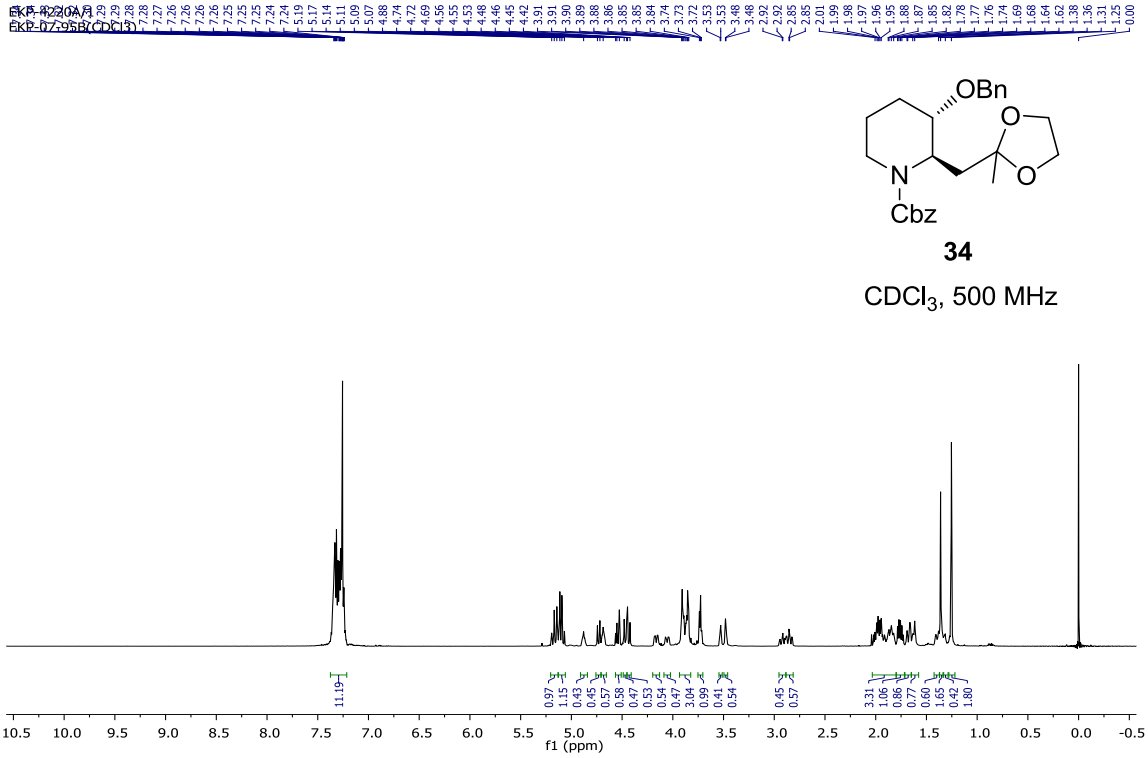
O
N
O
Cbz
33a
CDCl3, 75 MHz
f1 (ppm)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O
N
O
Cbz
34
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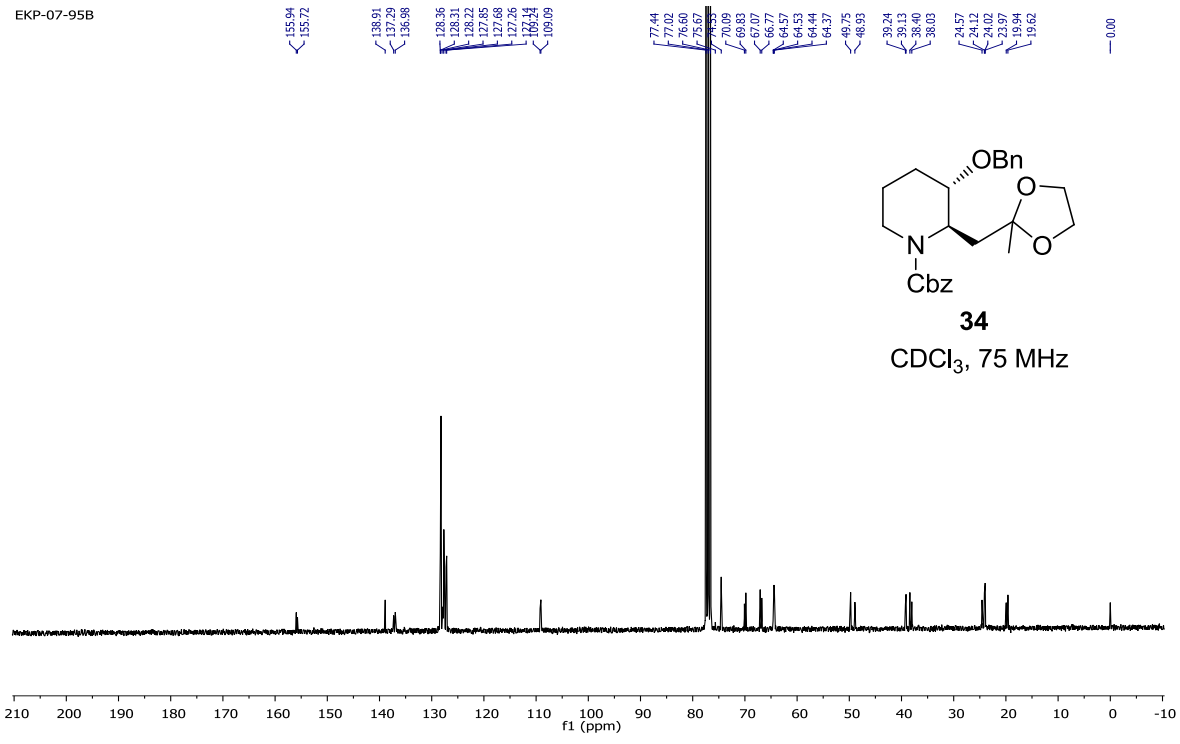
f1 (ppm)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Cbz
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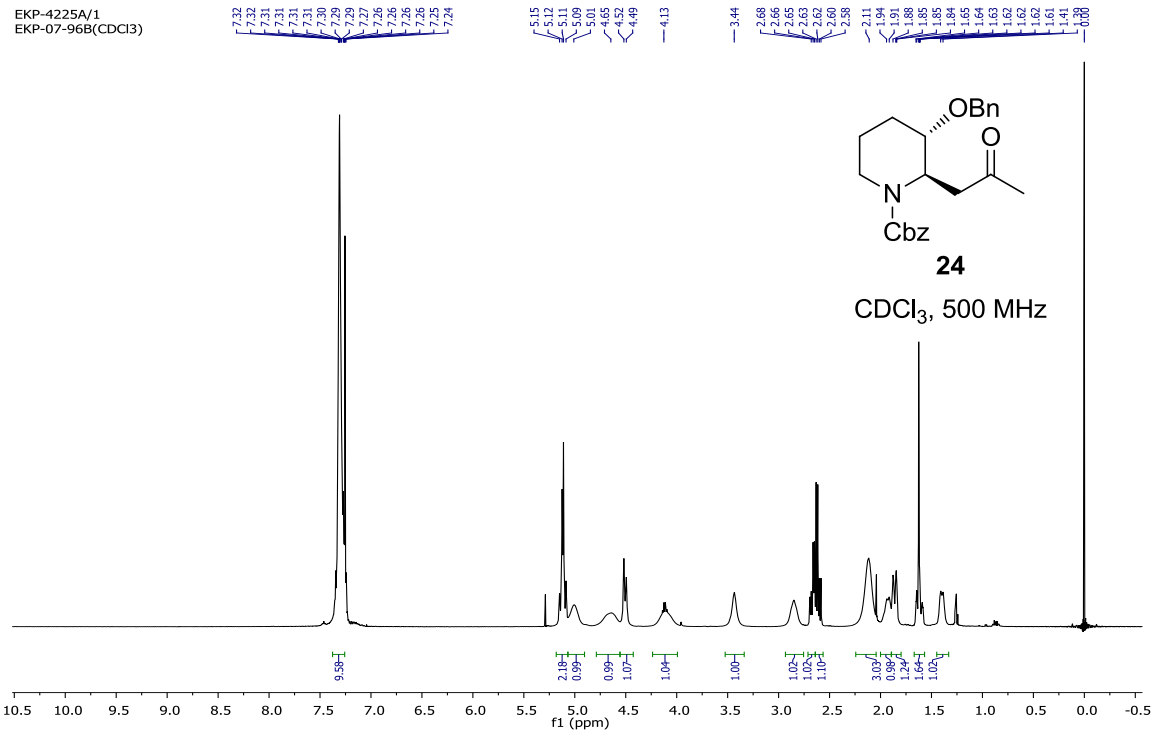
CDCl3, 75 MHz
f1 (ppm)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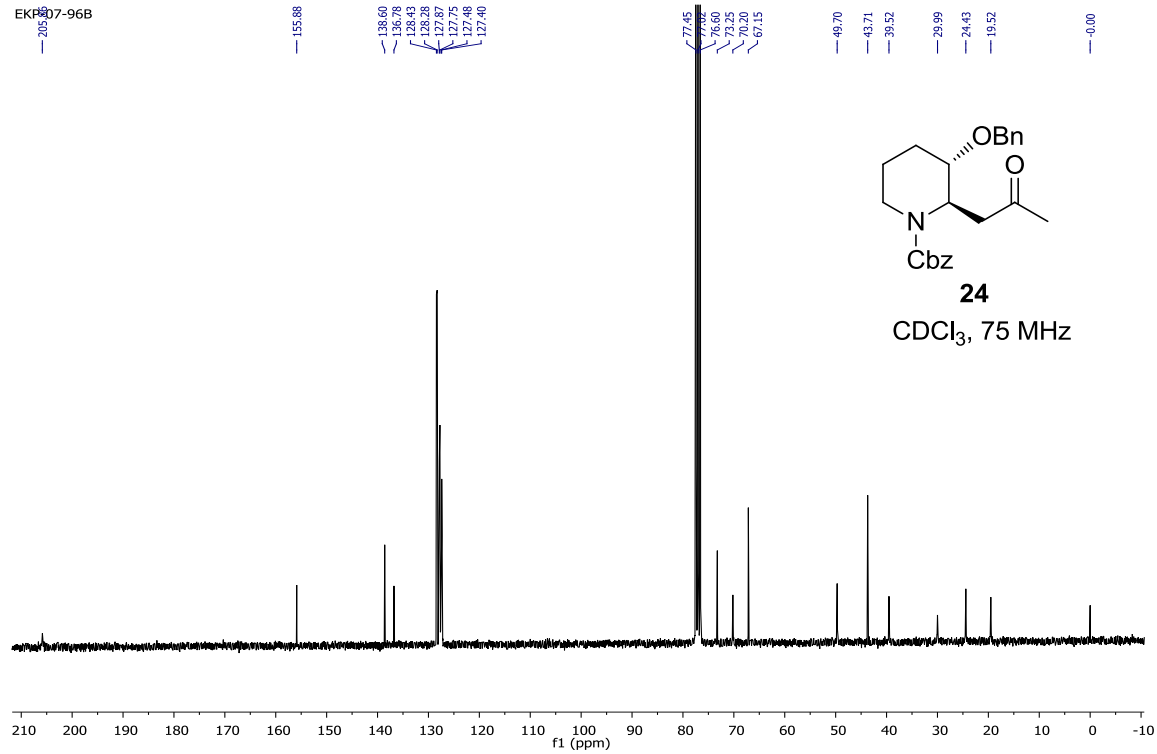
OBn
O
N
Cbz
24
CDCl3, 500 MHz
f1 (ppm)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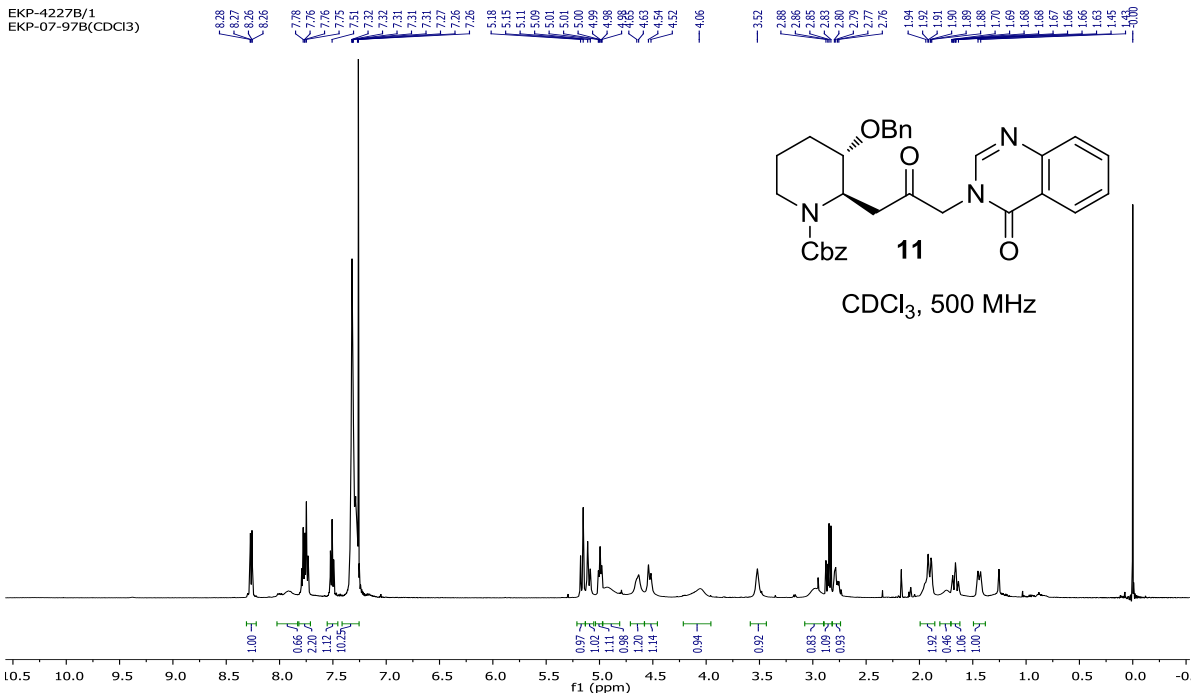
OBn
O
N
Cbz
24
CDCl3, 75 MHz
f1 (ppm)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N
Cbz
11
O
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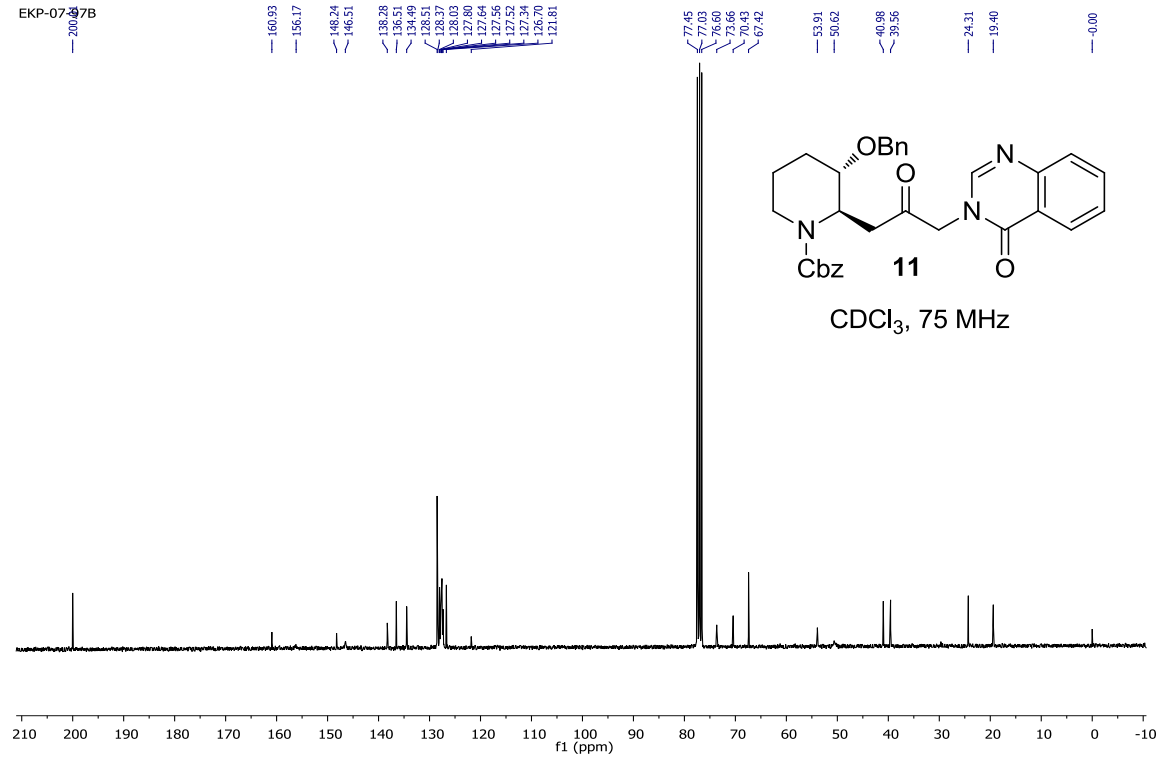
f1 (ppm)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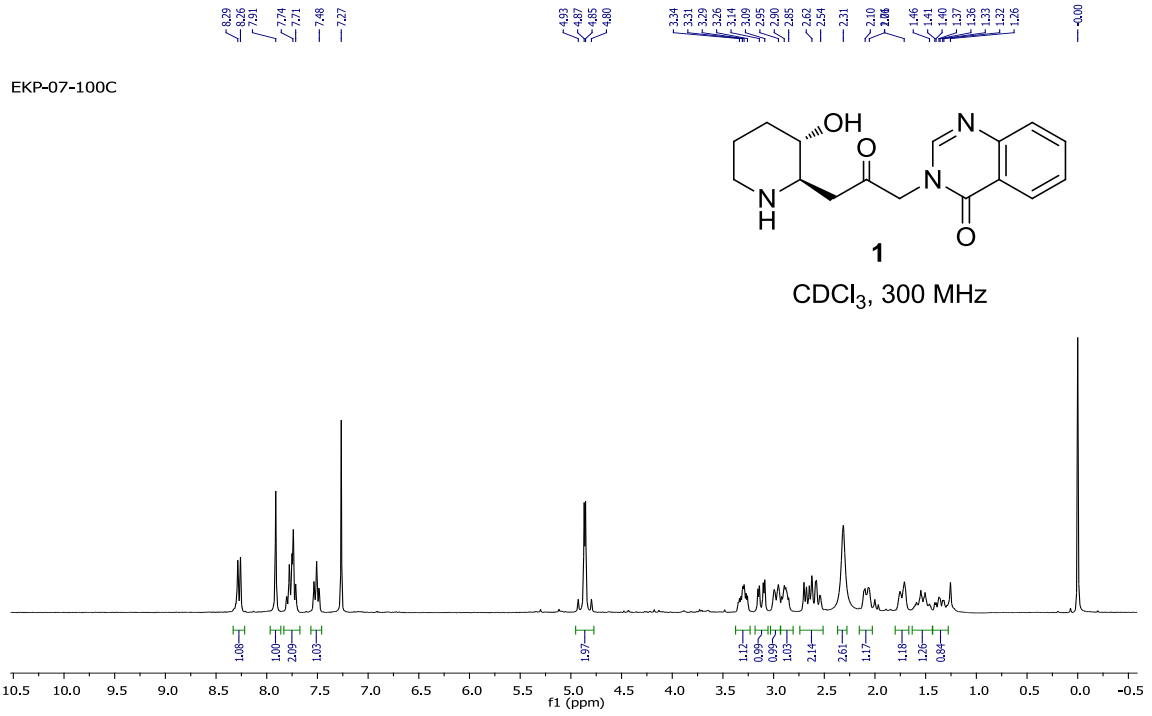
OBn
O
N
N
Cbz
11
O
CDCl3, 75 MHz
f1 (ppm)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N
H
N
O
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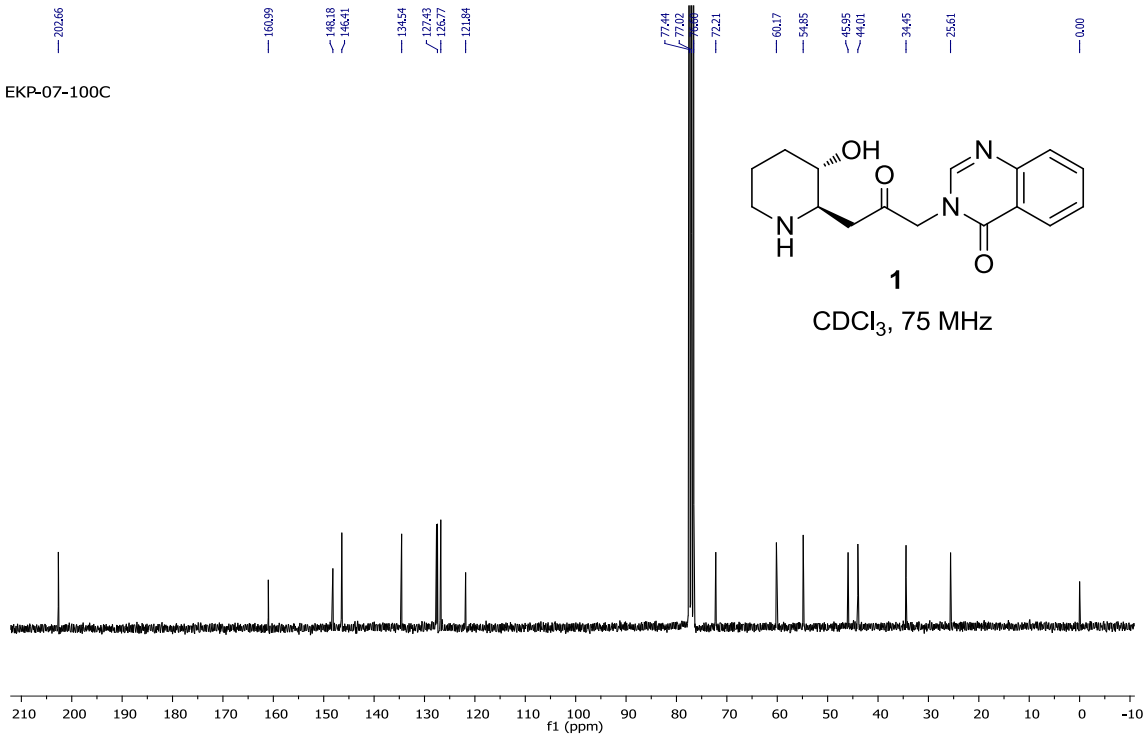
f1 (ppm)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H
N
O
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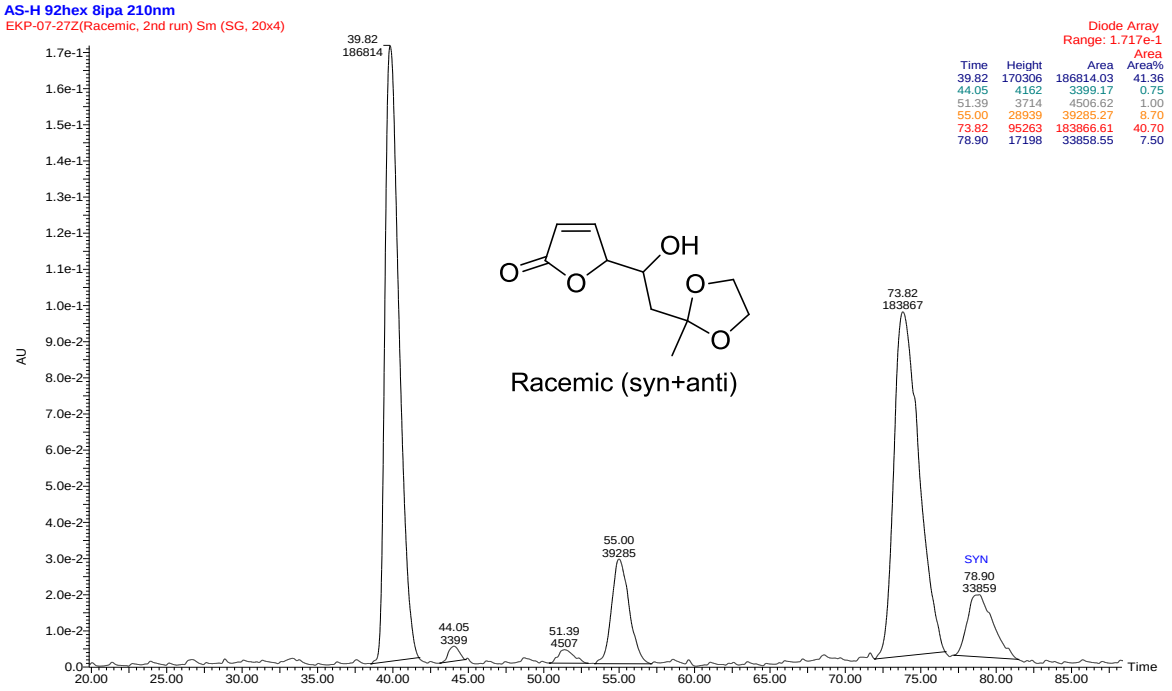
CDCl3, 75 MHz
f1 (ppm)

4.8 Selected HPLC chromatograms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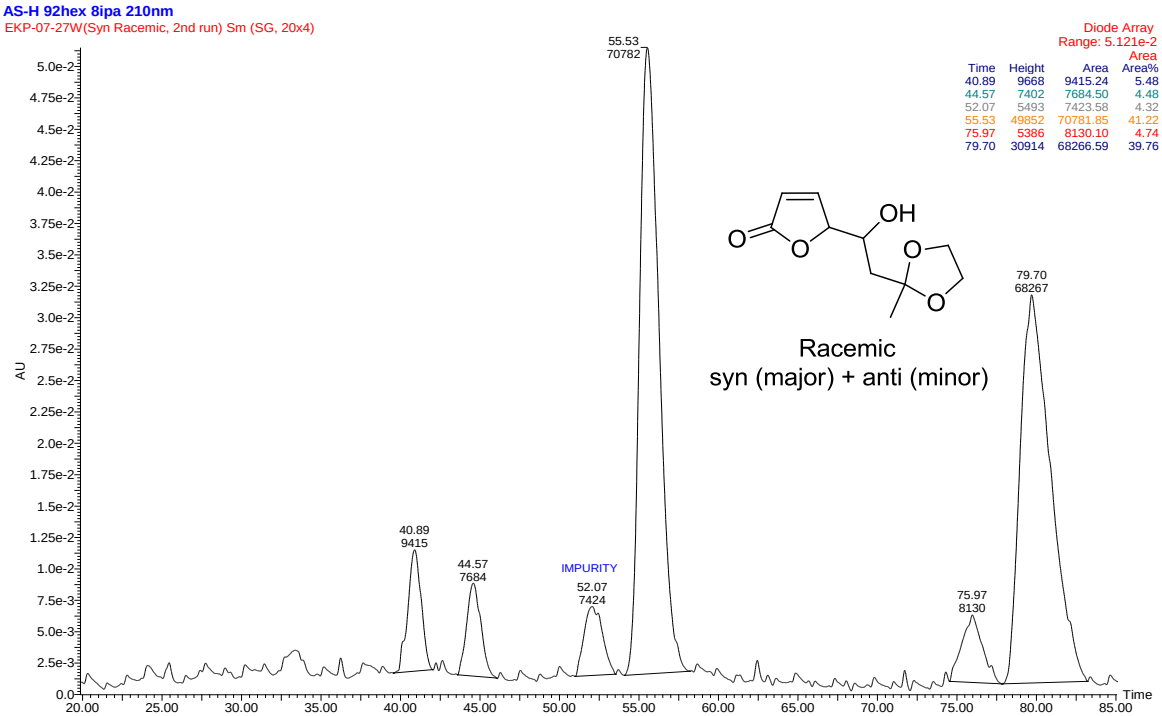
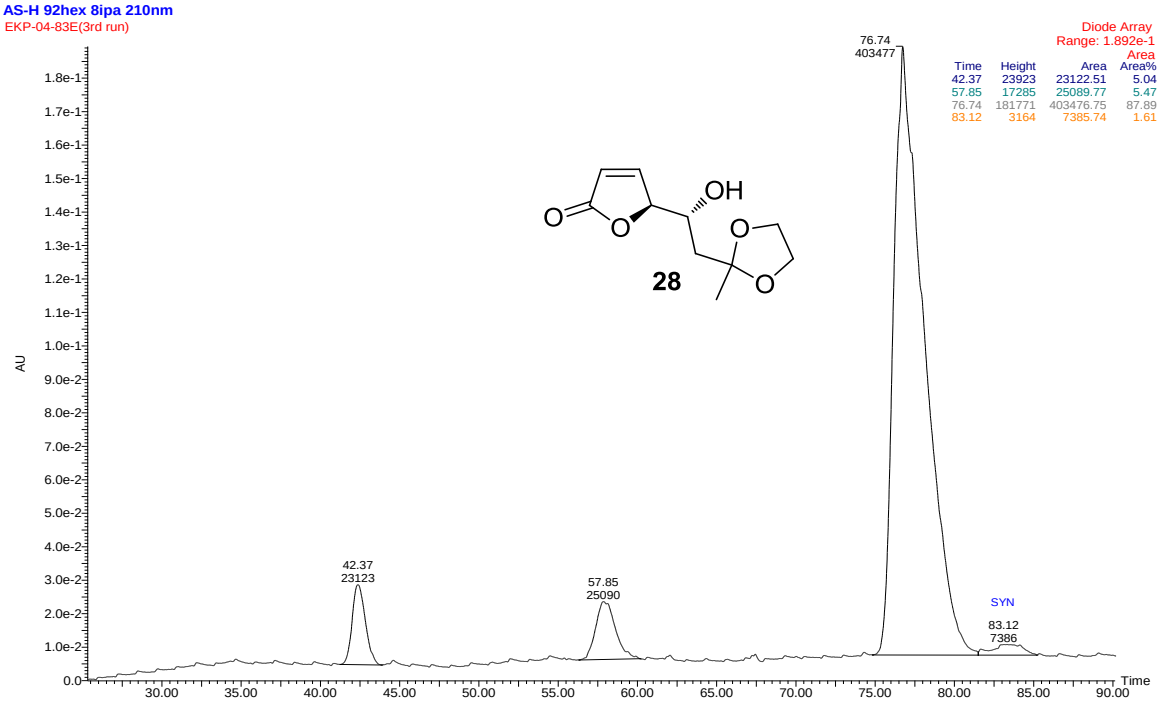
EKP-07-27Z(Racemic, 2nd run) Sm (SG, 20x4)
Diode Array
Range: 1.717e-1
Area
Time Height Area Area%
39.82 170306 186814.03 41.36
44.05 4162 3399.17 0.75
51.39 3714 4506.62 1.00
55.00 28939 39285.27 8.70
73.82 95263 183866.61 40.70
78.90 17198 33858.55 7.50
39.82
186814
73.82
183867
55.00
39285
SYN
78.90
33859
44.05
3399
51.39
4507
OH
O
O
O
O
Racemic (syn+anti)
AU
Time


AS-H 92hex 8ipa 210nm
EKP-07-27W(Syn Racemic, 2nd run) Sm (SG, 20x4)
Diode Array
Range: 5.121e-2
Area
Time Height Area Area%
40.89 9668 9415.24 5.48
44.57 7402 7684.50 4.48
52.07 5493 7423.58 4.32
55.53 49852 70781.85 41.22
75.97 5386 8130.10 4.74
79.70 30914 68266.59 39.76
55.53
70782
79.70
68267
40.89
9415
44.57
7684
IMPURITY
52.07
7424
75.97
8130
OH
O
O
O
O
Racemic
syn (major) + anti (minor)
AU
Time

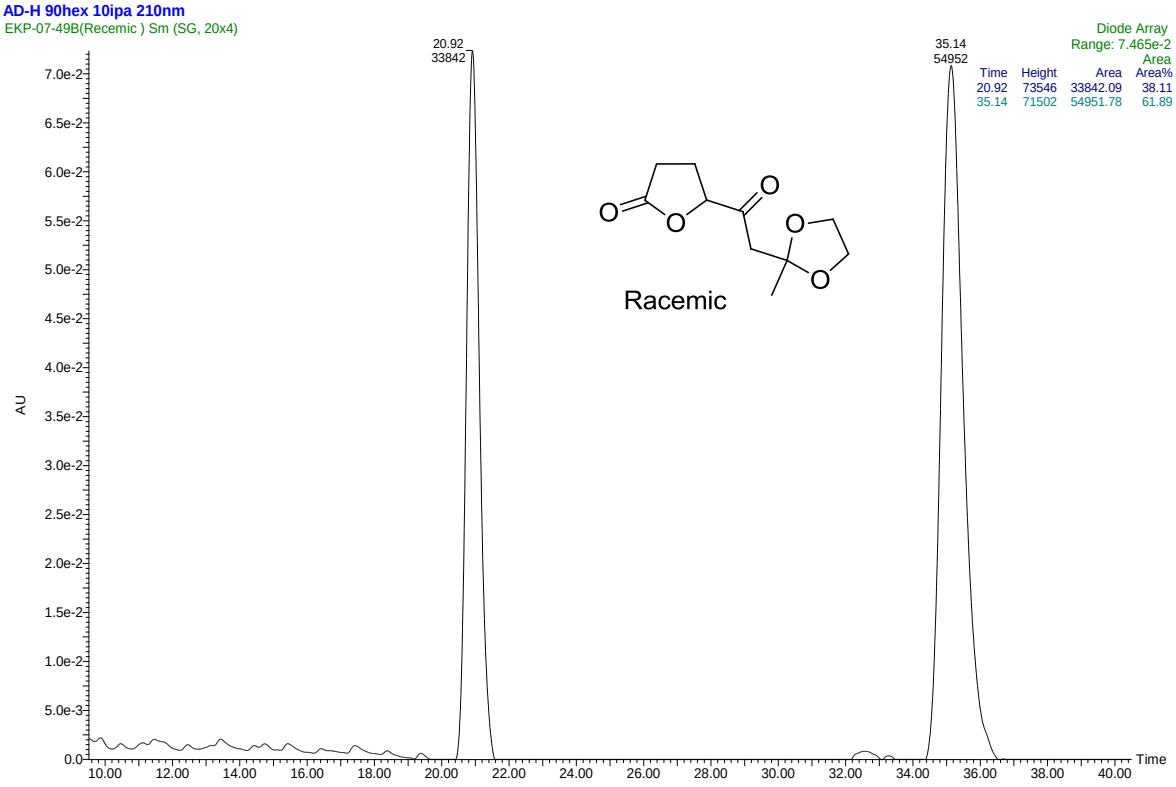
AS-H 92hex 8ipa 210nm

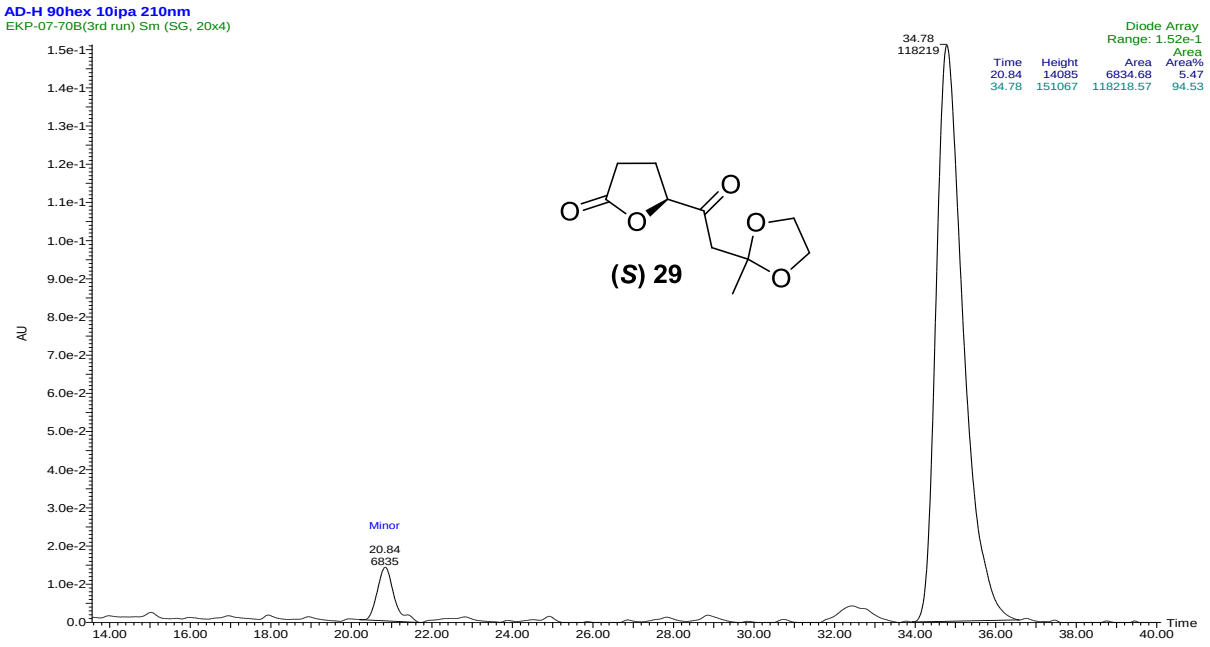
EKP-04-83E(3rd run)

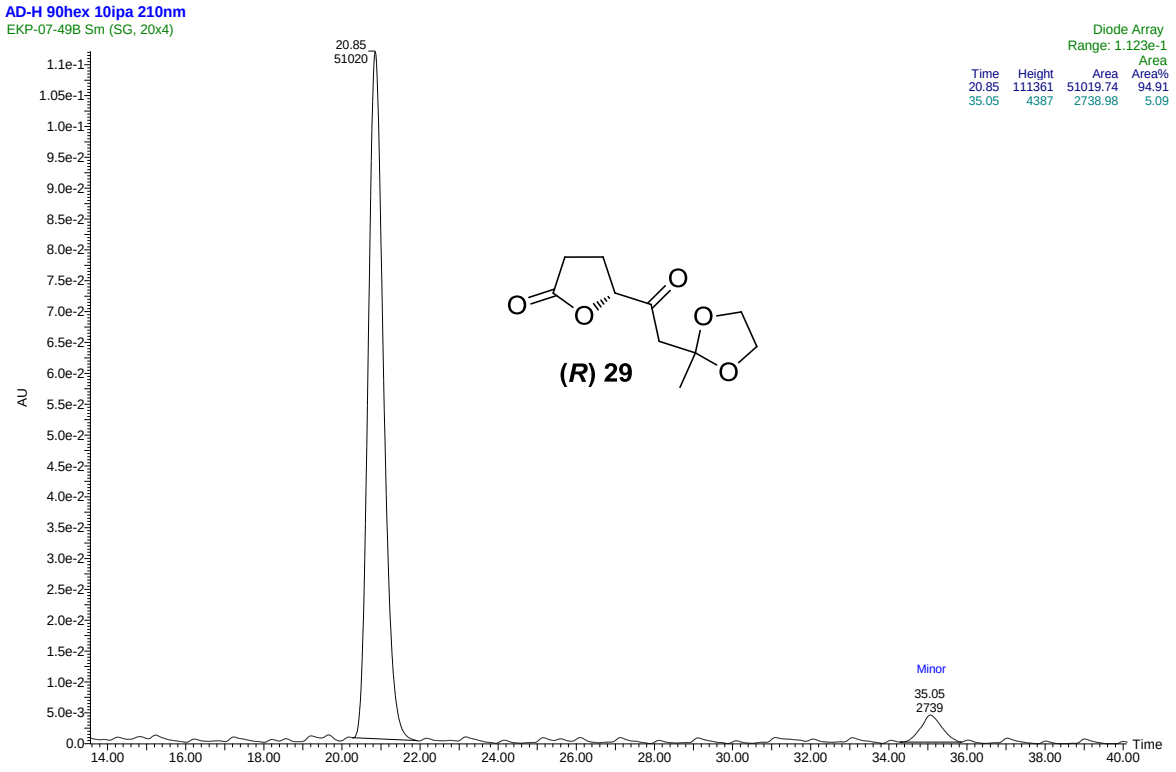


AD-H 90hex 10ipa 210nm

EKP-07-49B(Recemic) Sm (SG, 20x4)




AD-H 90hex 10ipa 210nm
EKP-07-70B(3rd run) Sm (SG, 20x4)
Diode Array
Range: 1.52e-1
Area
Time Height Area Area%
20.84 14085 6834.68 5.47
34.78 151067 118218.57 94.53
34.78
118219
(S) 29
Minor
20.84
6835
AU
Time

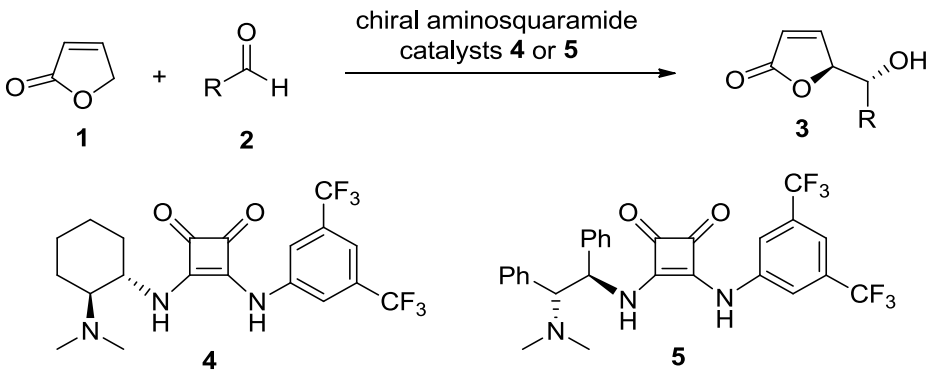

AD-H 90hex 10ipa 210nm
EKP-07-49B Sm (SG, 20x4)
Diode Array
Range: 1.123e-1
Area
Time Height Area Area%
20.85 111361 51019.74 94.91
35.05 4387 2738.98 5.09
20.85
51020
(R) 29
Minor
35.05
2739
AU
Time

CHAPTER 5

Conclusions

5.1 Summary of the thesis

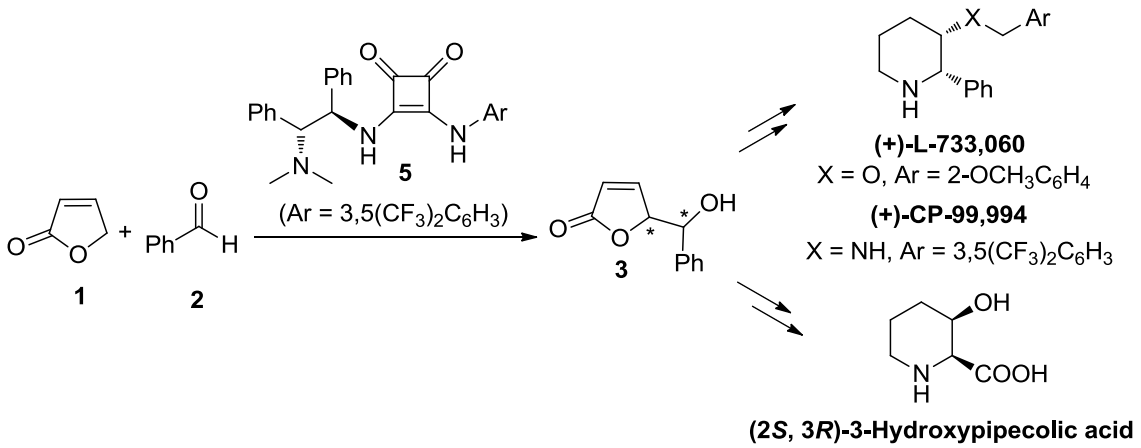
The organocatalytic direct vinylogous aldol (ODVA) reactions of γ-crotonolactone with various aromatic aldehydes (Scheme 5.1) were developed. It was observed that these reactions were catalyzed by several bifunctional chiral aminothioureas and aminosquaramides. A catalyst survey was carried out to find the optimal catalyst. Among various thiourea and squaramide catalysts, the squaramide catalysts gave the best result, providing the *anti* diastereomer as the major product. The optimized conditions were employed in a study of the scope of the reaction with a variety of aldehydes. These investigations indicated that the choice of catalyst **4** or **5** was determined by the nature of the aldehyde and high enantioselectivities were obtained by proper pairing of the catalyst and aldehyde. Overall, good diastereoselectivities (5-8:1) and excellent enantioselectivities (94- >99% *ee*) were obtained. Chapter 2 of this thesis describes details of the development of this method. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.



Scheme 5.1. The ODVA reaction catalyzed by squaramides **4** and **5**.

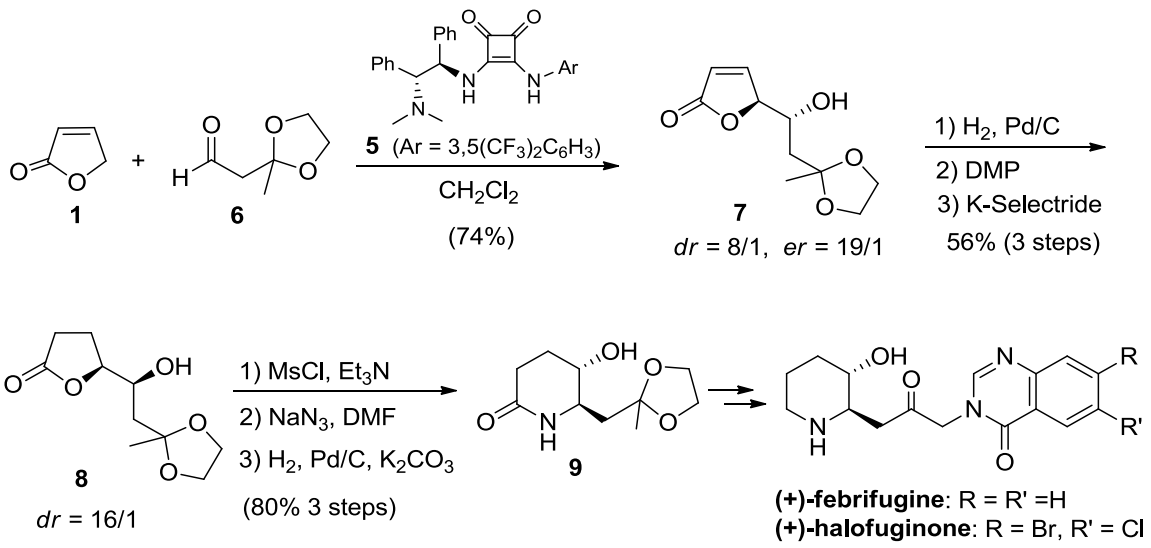
To demonstrate the synthetic importance of the organocatalytic direct vinylogous aldol (ODVA) reactions of *γ*-crotonolactone with aldehydes, application of the methodology in the synthesis of 2,3-disubstituted piperidines such as (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid was examined. The substance P receptor antagonists (+)-L-733,060 and (+)-CP-99,994, are associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission and (2*S*,3*R*)-3-hydroxypipecolic acid, is a component of tetrazomine, an antitumor agent and an antibiotic. In this project, ODVA reaction of *γ*-crotonolactone with benzaldehyde as the key step provided an efficient entry into piperidine derivatives (Scheme 5.2). The synthesis of (+)-L-733,060 was accomplished in 9 steps from the *γ*-crotonolactone (**1**) in 24.8% overall yield. The synthesis of (+)-CP-99,994 was accomplished in 11 steps from the *γ*-crotonolactone (**1**) in 16.9% overall yield. The synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid was accomplished in 10 steps from the *γ*-crotonolactone (**1**) in 28.1% overall yield. The results of this work are presented in

Chapter 3 of this thesis. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.



Scheme 5.2. Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid.

In the last project, the ODVA reaction was employed in the total synthesis of the antimalarial alkaloid (+)-febrifugine and a formal synthesis of (+)-halofuginone, an antimalarial agent (Scheme 5.3). The key steps in the synthesis involve the ODVA reaction of *γ*-crotonolactone with the aldehyde **6** and the isomerization of a 2-aminoalkyl furanone to the 2,3-disubstituted piperidinone core **9** of the target. The synthesis of the (+)-febrifugine was accomplished in 14 steps from the commercially available *γ*-crotonolactone (**1**) in 6.8% overall yield. The results of this work are presented in Chapter 4 of this thesis. E. K. Paul contributed to all of the synthetic work and was involved in the preparation of the manuscript for publication.

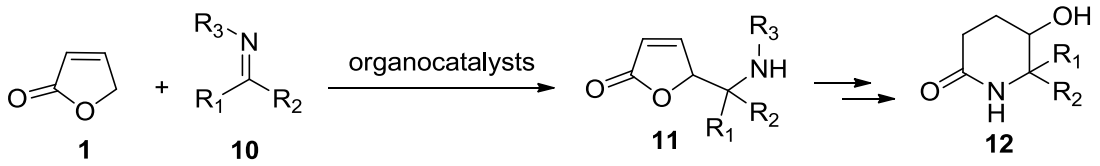


Scheme 5.3. Synthesis of (+)-febrifugine and a formal synthesis of (+)-halofuginone employing the ODVA reaction.

In summary, the thesis work has developed a highly enantioselective, organocatalytic direct vinylogous aldol reaction of crotonolactone with aldehydes. This methodology was used in the synthesis of various biologically active compounds and natural products containing the 2,3-disubstituted piperidine motif.

5.2 Future work

Although the products of the 2-furanone in ODVA reaction can be converted into piperidines, a limitation of the methodology is the need for converting the aldol products into the corresponding amino lactone. An attractive alternative to this approach would be the direct synthesis of the amino lactones **11** *via* an organocatalytic vinylogous Mannich reaction (Scheme 5.4) of imines **10** with 2-furanone.



Scheme 5.4. Organocatalytic direct vinylogous Mannich-type reaction of crotonolactone.

It is anticipated that, the Mannich reaction will be catalyzed by hydrogen bonding donor catalysts or by chiral protic acids depending on the nature of the amine used to make the imines.

Alternatively, instead of using a chiral catalyst, chiral imines can be used as substrates. In addition, the organocatalytic vinylogous aldol as well as Mannich reactions can be examined with a variety of substituted crotonolactones.